JAC Antimicrob Resist
https://doi.org/10.1093/jacamr/dlad042

JAC-Antimicrobial Resistance

Meningitis caused by extended-spectrum β-lactamase-producing *Escherichia coli* in infants in France: a case series

Gabriel Lignieres[1,2], Alexis Rybak [3,4], Corinne Levy [4,5,6,7], André Birgy[4,8], Stéphane Bechet[7], Stéphane Bonacorsi[4,8], Robert Cohen[4,5,7,9] and Fouad Madhi [1,4,5,*]

[1]Service de Pédiatrie Générale, Maladies Infectieuses et Médecine Interne, CHU Robert Debré, APHP, Paris, France; [2]Sorbonne Université, Paris, France; [3]Service des Urgences Pédiatriques, CHU Robert Debré, APHP, Paris, France; [4]Groupe de Pathologie Infectieuse Pédiatrique (GPIP) de la Société Française de Pédiatrie (SFP), Paris, France; [5]Université Paris Est, IMRB-GRC GEMINI, Créteil, France; [6]Centre de Recherche Clinique (CRC), Centre Hospitalier Intercommunal de Créteil, Créteil, France; [7]Association Clinique et Thérapeutique Infantile du Val-de-Marne (ACTIV), Créteil, France; [8]Service de Microbiologie, CHU Robert Debré, APHP, Centre National de Référence (CNR) associé Escherichia coli, Paris, France; [9]Unité Court Séjour, Petits nourrissons, Service de Néonatalogie, Centre Hospitalier Intercommunal de Créteil, Créteil, France

*Corresponding author. E-mail: Fouad.Madhi@chicreteil.fr

Received 1 November 2022; accepted 20 March 2023

Objectives: We report the first case series focusing on clinical and biological characteristics of meningitis caused by ESBL-producing *Escherichia coli* in infants.

Methods: Between 2001 and 2020, data on all cases of *E. coli* meningitis were prospectively collected from a network of 259 paediatric wards and 168 microbiology laboratories in France. We analysed the clinical and biological characteristics, short-term complications and long-term sequelae of ESBL-producing *E. coli* meningitis cases in patients <6 months old.

Results: In total, 548 cases of *E. coli* paediatric meningitis were reported. ESBL-producing *E. coli* represented 12 (2.2%) cases. We included 10 patients aged <6 months old. Eight (80%) patients presented at least one sign of clinical severity: six needed mechanical ventilation, three presented signs of shock and one was in a coma. The overall short-term prognosis was good, with only one meningitis-attributed death in the first hours of care. All surviving children received carbapenems for a median of 21 days (range 9–28). Two relapses occurred, including one in a patient who received only 14 days of imipenem. We reported no long-term sequelae at a median follow-up of 20 months.

Conclusions: Meropenem seems to be the treatment of choice for ESBL-producing *E. coli* meningitis in children and needs to be given as early as possible (<48 h) and for at least 21 days. Maternal colonization or infection with ESBL-producing Enterobacteriaceae needs to be reported to the neonatal or paediatric ICU team, in order to adapt the empirical antibiotic therapy.

Introduction

Escherichia coli is one of the leading bacterial species implicated in meningitis in infants, along with group B *Streptococcus* infection.[1–3] Moreover, among preterm infants, particularly very preterm infants, *E. coli* is the most common bacterium isolated.[4,5] In older children and adults, this pathogen is a rare cause of bacterial meningitis but may occur in immunocompromised patients or after neurosurgery.[6,7]

Bacterial meningitis is associated with high mortality and long-term sequelae,[1,8,9] and delay of adequate antibiotic therapy may lead to an unfavourable outcome.[10,11] This situation is mainly observed if the strain is resistant to the empirical antibiotic therapy. WT *E. coli* is ampicillin susceptible, but resistant strains keep increasing in prevalence, with almost 50% of isolates being resistant to aminopenicillins. They remain nonetheless susceptible to third-generation cephalosporins (3GCs) such as cefotaxime or ceftriaxone, which are the cornerstone for treating severe infections due to *E. coli*.

Although the first descriptions of ESBL-producing Enterobacteriaceae were reported in 1980, this phenomenon became a public health problem in the 2000s in many countries. Now, *E. coli* accounts for most of the community-acquired infections due to ESBL-producing Enterobacteriaceae.[12] Severe

infections involving ESBL-producing *E. coli* (ESBL-E) may lead to increased mortality and long-term sequelae, especially in the event of empirical treatment failure. In France, 3GCs are recommended as empirical therapy for bacterial meningitis and are prescribed in more than 95% of *E. coli* meningitis cases before receiving the antibiotic susceptibility pattern results.[13–15]

ESBL-E faecal carriage has increased from 5% to 10% in the French community population over the last 10 years, in adults and in children.[16,17] However, disparities exist worldwide, because the share of ESBL-producing Enterobacteriaceae meningitis has been reported to be as high as 50% for *E. coli* meningitis and 80% for *Klebsiella* spp. meningitis in China.[1,2] This expansion has been mostly attributed to the overuse of cephalosporins and quinolones.[16] Recently, a worrying proportion of newborns and their mothers have been reported to be colonized with ESBL-E in European countries,[18,19] raising fears of an increasing number of ESBL-E infections in newborns and infants. Yet, despite an evident increase in *E. coli* resistance, bacterial meningitis cases involving ESBL-E have been reported in only a few case reports or observational studies, focused on epidemiological rather than clinical data.[10,20–22]

By using the data from an active surveillance network of paediatric bacterial meningitis cases coordinated by the Association Clinique et Thérapeutique Infantile du Val-de-Marne (ACTIV) group and the Paediatric Infectious Diseases Group of the French Paediatric Society, from 2001 to 2020 in France, we aimed to describe the clinical and biological characteristics, short-term complications and long-term sequelae of ESBL-E meningitis cases reported in children <6 months old.

Materials and methods

From January 2001 to December 2020, 259 paediatric wards and 168 microbiology laboratories prospectively enrolled all reported cases of meningitis in children <18 years old throughout France. The methodology of this active surveillance system was previously described.[23] ESBL-E meningitis cases were identified when an ESBL-producing isolate was reported by the local investigator. In our study, we only included children <6 months old diagnosed with ESBL-E meningitis. Older children were excluded because of specific risk factors such as CSF shunt or immunodeficiency, which needed specific medical and surgical care.

The diagnosis of meningitis was based on a positive CSF culture or positive PCR result for CSF, with or without pleocytosis (≥10 cells/μL in children >28 days old and ≥20 cells/μL in children ≤28 days old)[24] and/or pleocytosis in CSF associated with positive blood culture and clinical signs suggesting meningitis. Bacterial isolate identification, antibiotic susceptibility pattern and K1 capsular antigen determination were performed by local microbiology centres using standard methods. Antibiotic susceptibility testing was interpreted by using the Comité de l'antibiogramme de la Société Française de Microbiologie (CASFM)/EUCAST guidelines.[25]

Early-onset sepsis (EOS) and late-onset sepsis were defined as occurring in the first 3 days of life and from 3 to 90 days of life, respectively.[26] Infants were considered preterm if born <37 weeks and very preterm if born <32 weeks.

Signs for clinical severity included shock, coma and the need for mechanical ventilation. Shock was defined according to international guidelines.[27,28] Short-term complications, such as seizures, intracranial bleeding, cerebral venous thrombosis, brain empyema or relapse were noted by the local investigator. Relapse was defined as a new diagnosis of meningitis within 3 weeks after completing initial treatment. Long-term sequelae were screened with brain MRI, audiometry and during follow-up consultations. The follow-up duration corresponded to the last reported consultation.

The data collection was approved by the French National Data Protection Commission (no. 913006) and the study was registered at ClinicalTrials.gov (NCT04664569).

Results

Study population

Between 2001 and 2020, 548 cases of *E. coli* paediatric bacterial meningitis were reported. ESBL-E was reported in 12 (2.2%) cases. During the study period, no significant trend was found and the number of ESBL-E meningitis cases ranged from 0 in 2001 to 2 in 2020 (Figure 1). Among the 12 cases, we excluded 2 patients aged >6 months. These patients were 2 and 12 years old, both presenting a prior CSF shunt. They both received a combination of meropenem and fosfomycin for 28 days, and the second patient received intrathecal gentamicin for 2 days. The long-term evolution was good for both patients, despite early complications for the 12-year-old patient: ventriculitis and extradural empyema on Day 7 with the need for a new surgical extraventricular CSF shunt.

Our 10 included cases corresponded to 3 patients with EOS and 6 with late-onset sepsis. The remaining patient was 4 months old (129 days old) at meningitis diagnosis. The median age at meningitis onset was 8 days (range 1–129) and the median term of birth was 38 weeks (24–41) (Table 1).

In 6 (60%) cases, the mother received intrapartum antibiotic therapy: amoxicillin in 5 cases and ceftriaxone in 1 case. The reasons for this intrapartum antibiotic therapy were prophylaxis for group B *Streptococcus* disease in four cases and fever during childbirth or in the previous days in two. Data on maternal ESBL-E colonization were not reported in medical records.

Clinical and biological signs

Initial symptoms leading to meningitis diagnosis are described in Table 1. They were fever or hypothermia in seven cases, acute respiratory distress in four, shock in three and neurological signs including hypotonia, bulging fontanelle or coma in four. In one case, the only reported symptom was hyperglycaemia in the hours before the meningitis appeared. At the time of meningitis diagnosis, in 4 (40%) cases, the C-reactive protein level was <40 mg/L, but the overall initial median C-reactive protein level was 66 mg/L (range 3–309). Procalcitonin level was documented in only two patients and was altered for both (3.1 and 16.4 ng/mL).

CSF analysis and blood and urine culture are described in Table 2. The meningitis diagnosis was established on positive CSF culture in 7 (70%) cases, positive PCR results in CSF with suggestive clinical signs in 1 case, and positive blood culture with CSF pleocytosis and suggestive clinical signs in 2 cases. The median CSF leucocyte count was 87 elements/mL (range 3–12 000). In three cases, the CSF leucocyte count was <10 elements/mL, but Gram staining was positive for Gram-negative rods in two of these cases, and the CSF culture was positive for ESBL-E in all three cases. From non-haemorrhagic lumbar punctures, the median CSF protein level was 1.07 g/L (range 0.27–2.30) and median

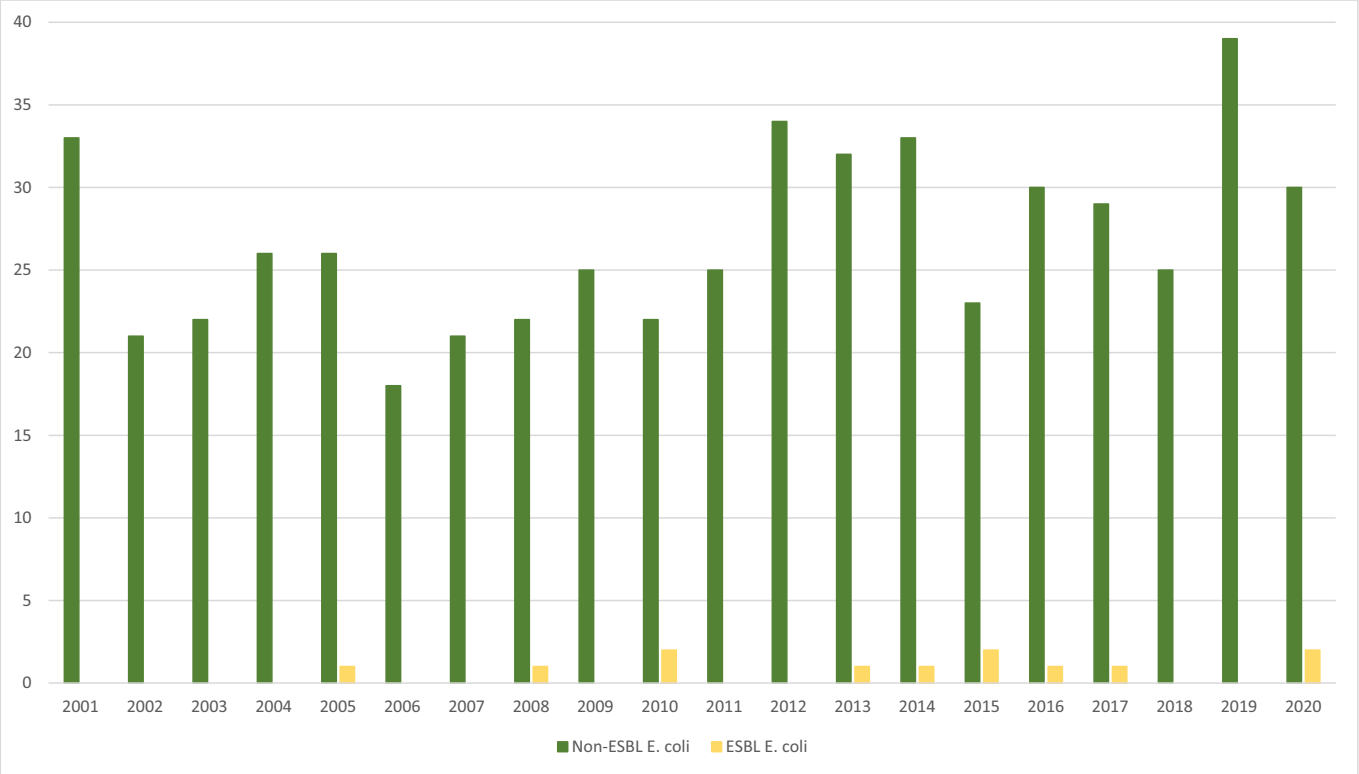

Figure 1. Evolution of ESBL-producing and non-ESBL-producing *E. coli* meningitis by year.

CSF glucose level 2.45 mmol/L (range 0.4–16.5). K1 antigen was positive in 7 (70%) cases.

A second lumbar puncture was performed in 5 (50%) cases, at a median of 3 days (range 2–4) after the initial lumbar puncture.

Empirical and definitive antibiotic therapy

Empirical and definitive antibiotic therapy is described in Table 3. After antibiotic susceptibility test results, all patients (except the one child who died in the first hours of care) received a carbapenem (meropenem or imipenem) for a median of 21 days (range 9–28). Aminoglycosides were prescribed in all cases for a median of 4.5 days (1–7). Ciprofloxacin was added in 5 (50%) cases for a median of 21 days (5–21). In one case (Patient 5 in the tables), the strain was resistant to ciprofloxacin, yet the patient received 21 days of ciprofloxacin.

The median total duration of antibiotic therapy was 21 days (range 14–28), excluding the patient who died in the first hours of care.

Antibiotic susceptibility patterns

Antibiotic susceptibility patterns are presented in Table 4. All ESBL-E strains were susceptible to the carbapenem, 90% to amikacin and only 44.4% to ciprofloxacin. Among the five tested strains, all were susceptible to fosfomycin. Remarkably, the two relapses had the same antibiotic susceptibility pattern as the initial meningitis case.

Short-term complications and long-term sequelae

Clinical severity, short-term complications, long-term sequelae and follow-up are described in Table 5. Eight (80%) cases presented at least one sign of clinical severity: six needed mechanical ventilation, three patients presented signs of shock and one patient was in a coma. In two cases, preterm infants experienced intraventricular haemorrhage (grade 1 or 2) during treatment. For the two children with relapse, complications were reported: grade 2 intraventricular haemorrhage and subdural haematoma with the need for extraventricular derivation.

Among all patients, one died from septic shock in the first 24 h after meningitis diagnosis. Another one died 2 months after meningitis resolution due to an HSCT graft failure for familial haemophagocytic lymphohistiocytosis.

Among the survivors for whom long-term follow-up data were available, no sequelae (including hearing loss and neurological impairment) were described. The median follow-up was 20 months (range 6–64).

Relapses

Relapses are described in Tables 1–3 and 5. Two children were concerned: the first received only 14 days of imipenem for the initial meningitis, but no reason for relapse was found for the second patient. Both strains were susceptible to carbapenems, amikacin and fosfomycin but resistant to ciprofloxacin. Both children received a combination of meropenem and fosfomycin to treat the relapse.

Table 1. Study population and clinical features at meningitis diagnosis

Case	Sex	Term of birth (weeks)	Birth weight (g)	Risk factors	Age at meningitis diagnosis (days)	Symptoms at meningitis diagnosis
1	M	30	1075	—	6	Hyperglycaemia
2	M	40	3240	FHL (but diagnosed after the meningitis)	23	Fever + tachycardia
3	F	24	590	—	1	Hypothermia + acute respiratory distress
4	F	30	1400	—	12	Acute respiratory distress
5	M	39	3140	—	12	Fever + shock
6	M	41	3710	—	10	Fever + axial hypotonia + vomiting
7	M	40	3930	—	129	Fever + shock + bulging fontanelle
8	F	32	1975	—	1	Bradycardia + desaturation
8 (R)	F	32	1975	—	17	Fever + tachycardia
9	F	39	2500	Gastric sample at birth positive for ESBL-E	5	Acute respiratory distress + coma
10	M	37	3800	—	1	Fever + axial hypotonia + acute respiratory distress
10 (R)	M	37	3800	—	36	Fever + shock + acute respiratory distress + fainting

M, male; F, female; FHL, familial haemophagocytic lymphohistiocytosis; (R), relapse.

Discussion

To our knowledge, our study is the first published case series focusing on ESBL-E meningitis in infants, with 10 cases between 2001 and 2020. Our study highlights that an early switch to adequate antibiotic therapy and its continuation for at least 21 days led to a fair prognosis for ESBL-E meningitis in these children. Most cases (including the two relapses) were treated with a carbapenem (meropenem or imipenem), which seems to be the antibiotic class of choice for ESBL-E meningitis. The time to initiate adequate antibiotic therapy should be as short as possible, ideally less than 48 h. Rapid ESBL detection tests can be used to minimize this delay. Antibiotic therapy also needs to be continued for at least 21 days because the only case treated for only 14 days exhibited relapse in the days after antibiotic discontinuation.

Among carbapenems, meropenem seems the most suited to treat ESBL-E meningitis in infants. The MIC epidemiological cut-off value for *E. coli* is lower for meropenem than imipenem (0.06 versus 0.5 mg/L, respectively).[29] Remarkably, in neonates and infants <90 days old, the individual dose of meropenem might vary from 20 to 40 mg/kg every 8 h depending on the clinical response and strain MIC.[30] Imipenem associated with cilastatin is also said to be more epileptogenic, although recent studies and a meta-analysis reported data to the contrary.[31,32] A prospective study could help compare these two treatments for ESBL-E meningitis but may be difficult to organize because of the very low prevalence of these infections in children.

Aminoglycosides were used in all cases as adjuvant therapy at a median of 4.5 days (range 1–7). Although aminoglycosides have particularly poor CSF diffusion, they are useful to obtain rapid bactericidal activity when bacteraemia is associated.[33] Ciprofloxacin was frequently used (50%) combined with carbapenems, even if in one case the strain was resistant to fluoroquinolones. Some teams use ciprofloxacin combined with a β-lactam antibiotic to prevent short-term neurological complications such as empyema. However, a recent study showed no advantage of combining ciprofloxacin with a 3GC for treating *E. coli* meningitis in children in terms of improving short-term neurological outcomes and mortality.[34]

Current French guidelines support the choice of amoxicillin and gentamicin for non-severe suspected EOS and cefotaxime and gentamicin for severe suspected EOS.[35] For suspected *E. coli* meningitis, the recommended empirical treatment is 3GCs and an aminoglycoside.[13,14] In total, 2.2% of our isolated strains in *E. coli* meningitis were ESBL producers. This proportion is consistent with that observed in maternal–fetal colonization,[18] but is less frequent than in urinary tract infections in children.[12,36] ESBL-E rates are important to monitor because a higher proportion could lead to replacing 3GCs with carbapenems as the preferred empirical therapy for neonatal Gram-negative rod meningitis.[2] However, our data favour maintaining the current guidelines in France.

Information on maternal ESBL-E colonization before childbirth might lead physicians to consider carbapenems for empirical therapy in young infants with a meningitis diagnosis. The systematic search for maternal carriage of ESBL does not seem necessary in France but may be discussed in countries or regions with a high prevalence of ESBL infections. Nonetheless, if known, recent maternal infection or colonization with ESBL-E needs to be reported to the neonatal or paediatric ICU team, to adapt empirical antibiotic therapy.

The main limitation of our study is the small number of patients included. Furthermore, although the prevalence of ESBL-E meningitis seems very low in France, we cannot exclude that some cases may not have been reported to the meningitis observatory.

Table 2. CSF analysis and blood and urine culture

Case	CSF leucocyte count (elements/mL)	CSF neutrophil count (elements/mL)	CSF protein level (g/L)	CSF glucose level (mmol/L)	CSF Gram stain	CSF culture	Blood culture	Urine culture	K1 antigen	Second LP	Second LP timing (days)
1	4	0	0.72	16.5	Negative	ESBL-E	ESBL-E	—	No	—	—
2	3	0	0.42	1.9	GNR	ESBL-E	Negative	—	No	NP	—
3	124	97	2.4	2.3	Negative	Negative	ESBL-E	—	Auto-agglutinating strain	Negative	4
4	8	0	1.54	4.8	GNR	ESBL-E	ESBL-E	—	Yes	Positive	3
5	650	611	0.86	5.1	Negative	ESBL-E	ESBL-E	ESBL-E	No	Negative	4
6	4050	1012	1.28	1.5	GNR	ESBL-E	ESBL-E	—	Yes	Negative	2
7	50	30	0.27	2.6	Negative	Negative	ESBL-E	Negative	Yes	NP	—
8	Haemorrhagic	Haemorrhagic	—	—	Negative	ESBL-E	ESBL-E	—	Yes	NP	—
8 (R)	1070	963	2.34	0.6	GNR	ESBL-E	ESBL-E	—	Yes	Negative	3
9	Haemorrhagic	Haemorrhagic	—	—	GNR	Negative (Positive PCR)	Negative	—	Yes	NP	—
10	12000	10560	2.3	0.4	GNR	ESBL-E	ESBL-E	—	Yes	Negative	3
10 (R)	5200	5148	7.3	0.5	GNR	ESBL-E	ESBL-E	—	Yes	Negative	3

GNR, Gram-negative rod; LP, lumbar puncture; NP, not performed; (R), relapse.

Table 3. Antibiotic therapy before meningitis diagnosis; empirical and definitive antibiotic therapy

Case	ATB after birth	Diagnosis before meningitis	Duration of ATB before meningitis (days)	Empirical ATB for meningitis	Duration of empirical ATB (days)	Definitive ATB for meningitis	Duration of carbapenems (days)	Duration of aminoglycosides (days)	Duration of CIP (days)	Duration of FOF (days)	Total ATB duration (days)
1	—	—		CAZ, VAN, NET, MTZ	1	—	—	—	—	—	1
2	CTX, AMX, GEN	EONI suspicion	8	—	—	MEM, AMK	21	4	—	—	21
3	—	—	—	CTX, GEN	2	MEM, CIP	28	2	21	—	28
4	CTX, GEN	EONI suspicion	2	—	—	IPM, CIP, AMK	21	6	21	—	21
5	AMC	Lymphangitis	4	CTX, GEN	1	MEM, CIP, GEN	21	7	21	—	21
6	—	—	—	AMC, GEN, CIP	1	MEM, CIP, GEN	21	5	5	—	21
7	—	—	—	CRO	1	MEM, CIP, AMK	9	4	21	—	21
8	—	—	—	CTX, AMX, GEN	1	IPM	14	1	—	—	14
8 (R)	—	—	—	IPM, GEN	1	MEM, FOF, GEN	21	3	—	14	21
9	AMX, GEN	EONI suspicion	2	CTX, VAN, MTZ, AMK	1	MEM, AMK	21	5	—	—	21
10	—	—	—	CTX, AMK	1	MEM, AMK	21	5	—	—	21
10 (R)	—	—	—	—	—	MEM, FOF	26	—	—	16	26

ATB, antibiotic therapy; AMK, amikacin; AMX, amoxicillin; AMC, amoxicillin/clavulanic acid; CAZ, ceftazidime; CIP, ciprofloxacin; CRO, ceftriaxone; CTX, cefotaxime; EONI, early-onset neonatal infection; FOF, fosfomycin; GEN, gentamicin; IPM, imipenem; MEM, meropenem; MTZ, metronidazole; NET, netilmicin; VAN, vancomycin; (R), relapse.

Table 4. Antibiotic susceptibility patterns for ESBL-producing *E. coli* meningitis in children

Antibiotics/ susceptibility	Susceptible (%)	Intermediate (%)	Resistant (%)
Piperacillin/ tazobactam ($n=7$)	71.4	28.4	0
Cefoxitin ($n=6$)	100	0	0
Cefotaxime ($n=9$)	0	11.1	88.9
Ceftazidime ($n=9$)	11.1	44.4	44.4
Cefepime ($n=7$)	0	42.9	57.1
Aztreonam ($n=5$)	0	20	80
Meropenem ($n=10$)	100	0	0
Amikacin ($n=10$)	90	0	10
Gentamicin ($n=9$)	66.7	0	33.3
Tobramycin ($n=8$)	50	0	50
Nalidixic acid ($n=9$)	44.4	0	55.6
Ciprofloxacin ($n=9$)	44.4	0	55.6
Fosfomycin ($n=5$)	100	0	0
Cotrimoxasole ($n=9$)	33.3	0	66.7

Another limitation is the lack of extended microbiological and genetic characterization of the strains involved. Unfortunately, too few strains were sent to the National Reference Centre for *E. coli* infections laboratory in Robert Debré hospital for further characterization.

Long-term follow-up was reported for all included cases, with a median follow-up of 20 months (range 5–64), and no neurological sequelae were reported for all patients. However, these sequelae might have been underestimated in our study by early evaluation. In fact, in another study, this complication was reported in 45% of children evaluated for childhood meningitis more than 5 years after discharge.[9]

Finally, signs of severity were more frequently reported in our study (78.6%), when compared with meningitis due to non-ESBL *E. coli* (37.8%) in another study.[13] However, the ESBL-E meningitis-attributed mortality rate in our study (1/10; 10%) was comparable to that of non-ESBL *E. coli* meningitis (9.2%).[13] Early appropriate antibiotic treatment, concerning 5/10 patients (and the 2 relapses) in our study, may explain this result. In adults with *E. coli* bacteraemia, mortality seems to be higher with ESBL-E than non-ESBL *E. coli* bacteraemic infection [OR 3.57 (95% CI 1.48–8.60)].[37] Increased mortality was probably due to

Table 5. Outcome and follow-up

Case	Clinical severity	Short-term complication	Long-term sequelae	Follow-up duration (months)	Death	Cause of death
1	Mechanical ventilation Shock	Unresponsive septic shock	—	—	Yes (at Day 1)	ESBL-producing *E. coli* meningitis
2	—	—	—	5	Yes (at 142 days of age)	HSCT graft failure for FHL
3	Mechanical ventilation	—	Normal brain MRI at 34 days No LT sequelae (including hearing loss)	41	—	—
4	Mechanical ventilation	Grade 1 intraventricular haemorrhage	Normal brain MRI at 30 days No LT sequelae (including hearing loss)	64	—	—
5	Shock	—	No LT sequelae	12	—	—
6	Mechanical ventilation	Cerebral venous thrombosis	No LT sequelae (including hearing loss)	37	—	—
7	Shock	—	No LT sequelae (including hearing loss)	17	—	—
8	Mechanical ventilation	Grade 1 intraventricular haemorrhage Relapse	No LT sequelae (including hearing loss)	21	—	—
8 (R)	Shock	Grade 2 intraventricular haemorrhage	No LT sequelae (including hearing loss)	20	—	—
9	Mechanical ventilation Coma	—	No LT sequelae	6	—	—
10	—	Relapse	Normal brain MRI at 12 days No LT sequelae (including hearing loss)	12	—	—
10 (R)	Mechanical ventilation Coma Shock	Subdural haematoma with need for an EVD	Normal brain MRI at 2 months No LT sequelae (including hearing loss)	12	—	—

FHL, familial haemophagocytic lymphohistiocytosis; LT, long-term; EVD, extraventricular drain; (R), relapse.

the delay of one or more days in receiving appropriate antibiotic treatment, which concerned 36/46 (78%) adults with ESBL-E *E. coli* infection versus 54/308 (17%) with non-ESBL *E. coli* infection.[37] In addition, a negative impact on outcomes of neonates with ESBL-E bacteraemia following inappropriate antibiotic treatment was reported in another study.[38]

Thus, our study suggests that good short-term prognosis can be achieved when appropriate antibiotic therapy with a susceptible drug is prescribed early and for at least 21 days. No long-term sequelae were reported in our study, but the follow-up duration might not have been long enough to detect them.

Conclusions

We describe here the first case series focusing on ESBL-E meningitis in children <6 months old published to date. Despite their severe initial presentation, the short-term prognosis was good for patients receiving carbapenems, with only one meningitis-attributed death. Carbapenems, especially meropenem, remain the treatment of choice for ESBL-E meningitis in children and need to be given as early as possible and for at least 21 days. Maternal ESBL-E infection or colonization could be an essential factor to investigate in further studies, especially in countries with high ESBL prevalence, in order to administer appropriate antibiotic therapy early to infants with suspected meningitis or sepsis.

Acknowledgements

We are very grateful to Laura Smales for her technical assistance. We also thank all of the French Pediatric Meningitis Network.

Funding

This study was supported by internal funding. The authors indicate that they have no financial relationships relevant to this article to disclose.

Transparency declarations

The authors declare that they have no competing interests.

References

1 Okike IO, Johnson AP, Henderson KL *et al*. Incidence, etiology, and outcome of bacterial meningitis in infants aged <90 days in the United Kingdom and Republic of Ireland: prospective, enhanced, national population-based surveillance. *Clin Infect Dis* 2014; **59**: e150–157. https://doi.org/10.1093/cid/ciu514

2 Jiang H, Su M, Kui L *et al*. Prevalence and antibiotic resistance profiles of cerebrospinal fluid pathogens in children with acute bacterial meningitis in Yunnan province, China, 2012-2015. *PLoS One* 2017; **12**: e0180161.

3 Ouchenir L, Renaud C, Khan S *et al*. The epidemiology, management, and outcomes of bacterial meningitis in infants. *Pediatrics* 2017; **140**: e20170476. https://doi.org/10.1542/peds.2017-0476

4 Schrag SJ, Farley MM, Petit S *et al*. Epidemiology of invasive early-onset neonatal sepsis, 2005 to 2014. *Pediatrics* 2016; **138**: e20162013. https://doi.org/10.1542/peds.2016-2013

5 Stoll BJ, Puopolo KM, Hansen NI *et al*. Early-onset neonatal sepsis 2015 to 2017, the rise of *Escherichia coli*, and the need for novel prevention strategies. *JAMA Pediatr* 2020; **174**: e200593. https://doi.org/10.1001/jamapediatrics.2020.0593

6 Bingen E, Levy C, de la Rocque F *et al*. Bacterial meningitis in children: a French prospective study. *Clin Infect Dis* 2005; **41**: 1059–63. https://doi.org/10.1086/432944

7 van de Beek D, Drake JM, Tunkel AR. Nosocomial bacterial meningitis. *N Engl J Med* 2010; **362**: 146–54. https://doi.org/10.1056/NEJMra0804573

8 Schiess N, Groce NE, Dua T. The impact and burden of neurological sequelae following bacterial meningitis: a narrative review. *Microorganisms* 2021; **9**: 900. https://doi.org/10.3390/microorganisms9050900

9 Chandran A, Herbert H, Misurski D *et al*. Long-term sequelae of childhood bacterial meningitis: an underappreciated problem. *Pediatr Infect Dis J* 2011; **30**: 3–6. https://doi.org/10.1097/INF.0b013e3181ef25f7

10 Boyer-Mariotte S, Duboc P, Bonacorsi S *et al*. CTX-M-15-producing *Escherichia coli* in fatal neonatal meningitis: failure of empirical chemotherapy. *J Antimicrob Chemother* 2008; **62**: 1472–4. https://doi.org/10.1093/jac/dkn362

11 Køster-Rasmussen R, Korshin A, Meyer CN. Antibiotic treatment delay and outcome in acute bacterial meningitis. *J Infect* 2008; **57**: 449–54. https://doi.org/10.1016/j.jinf.2008.09.033

12 Birgy A, Madhi F, Jung C *et al*. Diversity and trends in population structure of ESBL-producing Enterobacteriaceae in febrile urinary tract infections in children in France from 2014 to 2017. *J Antimicrob Chemother* 2020; **75**: 96–105. https://doi.org/10.1093/jac/dkz423

13 Basmaci R, Bonacorsi S, Bidet P *et al*. *Escherichia coli* meningitis features in 325 children from 2001 to 2013 in France. *Clin Infect Dis* 2015; **61**: 779–86. https://doi.org/10.1093/cid/civ367

14 Durrmeyer X, Cohen R, Bingen E *et al*. Therapeutic strategies for *Escherichia coli* neonatal meningitis. *Arch Pediatr* 2012; **19** Suppl 3: S140–144. https://doi.org/10.1016/S0929-693X(12)71288-5

15 NICE. Neonatal infection: antibiotics for prevention and treatment. https://www.nice.org.uk/guidance/ng195.

16 Birgy A, Levy C, Bidet P *et al*. ESBL-producing *Escherichia coli* ST131 versus non-ST131: evolution and risk factors of carriage among French children in the community between 2010 and 2015. *J Antimicrob Chemother* 2016; **71**: 2949–56. https://doi.org/10.1093/jac/dkw219

17 Woerther P-L, Burdet C, Chachaty E *et al*. Trends in human fecal carriage of extended-spectrum β-lactamases in the community: toward the globalization of CTX-M. *Clin Microbiol Rev* 2013; **26**: 744–58. https://doi.org/10.1128/CMR.00023-13

18 Birgy A, Mariani-Kurkdjian P, Bidet P *et al*. Characterization of extended-spectrum-beta-lactamase-producing *Escherichia coli* strains involved in maternal-fetal colonization: prevalence of *E. coli* ST131. *J Clin Microbiol* 2013; **51**: 1727–32. https://doi.org/10.1128/JCM.03255-12

19 Denkel LA, Schwab F, Kola A *et al*. The mother as most important risk factor for colonization of very low birth weight (VLBW) infants with extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-E). *J Antimicrob Chemother* 2014; **69**: 2230–7. https://doi.org/10.1093/jac/dku097

20 Moissenet D, Salauze B, Clermont O *et al*. Meningitis caused by *Escherichia coli* producing TEM-52 extended-spectrum beta-lactamase within an extensive outbreak in a neonatal ward: epidemiological investigation and characterization of the strain. *J Clin Microbiol* 2010; **48**: 2459–63. https://doi.org/10.1128/JCM.00529-10

21 Weissman SJ, Hansen NI, Zaterka-Baxter K *et al*. Emergence of antibiotic resistance-associated clones among *Escherichia coli* recovered from newborns with early-onset sepsis and meningitis in the United States, 2008-2009. *J Pediatric Infect Dis Soc* 2016; **5**: 269–76. https://doi.org/10.1093/jpids/piv013

22 Oldendorff F, Linnér A, Finder M *et al*. Case report: fatal outcome for a preterm newborn with meningitis caused by extended-spectrum

β-lactamase-producing *Escherichia coli* sequence type 1193. *Front Pediatr* 2022; **10**: 866762. https://doi.org/10.3389/fped.2022.866762

23 Ouldali N, Levy C, Varon E *et al*. Incidence of paediatric pneumococcal meningitis and emergence of new serotypes: a time-series analysis of a 16-year French national survey. *Lancet Infect Dis* 2018; **18**: 983–91. https://doi.org/10.1016/S1473-3099(18)30349-9

24 Kestenbaum LA, Ebberson J, Zorc JJ *et al*. Defining cerebrospinal fluid white blood cell count reference values in neonates and young infants. *Pediatrics* 2010; **125**: 257–64. https://doi.org/10.1542/peds.2009-1181

25 Vong O. CASFM/EUCAST V1.2 Octobre 2020. 2020. https://www.sfm-microbiologie.org/2020/10/02/casfm-eucast-v1-2-octobre-2020/.

26 Shane AL, Sánchez PJ, Stoll BJ. Neonatal sepsis. *Lancet* 2017; **390**: 1770–80. https://doi.org/10.1016/S0140-6736(17)31002-4

27 Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med* 2005; **6**: 2–8. https://doi.org/10.1097/01.PCC.0000149131.72248.E6

28 Weiss SL, Peters MJ, Alhazzani W *et al*. Surviving Sepsis Campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. *Pediatr Crit Care Med* 2020; **21**: e52–106. https://doi.org/10.1097/PCC.0000000000002197

29 MIC EUCAST. Antimicrobial wild type distributions of microorganisms. https://mic.eucast.org/search/?search%5Bmethod%5D=mic&search%5Bantibiotic%5D=-1&search%5Bspecies%5D=261&search%5Bdisk_content%5D=-1&search%5Blimit%5D=50&page=2.

30 Germovsek E, Lutsar I, Kipper K *et al*. Plasma and CSF pharmacokinetics of meropenem in neonates and young infants: results from the NeoMero studies. *J Antimicrob Chemother* 2018; **73**: 1908–16. https://doi.org/10.1093/jac/dky128

31 Hornik CP, Herring AH, Benjamin DK *et al*. Adverse events associated with meropenem versus imipenem/cilastatin therapy in a large retrospective cohort of hospitalized infants. *Pediatr Infect Dis J* 2013; **32**: 748–53. https://doi.org/10.1097/INF.0b013e31828be70b

32 Cannon JP, Lee TA, Clark NM *et al*. The risk of seizures among the carbapenems: a meta-analysis. *J Antimicrob Chemother* 2014; **69**: 2043–55. https://doi.org/10.1093/jac/dku111

33 Nau R, Sörgel F, Eiffert H. Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. *Clin Microbiol Rev* 2010; **23**: 858–83. https://doi.org/10.1128/CMR.00007-10

34 Tauzin M, Ouldali N, Lévy C *et al*. Combination therapy with ciprofloxacin and third-generation cephalosporin versus third-generation cephalosporin monotherapy in *Escherichia coli* meningitis in infants: a multicentre propensity score-matched observational study. *Clin Microbiol Infect* 2019; **25**: 1006–12. https://doi.org/10.1016/j.cmi.2018.12.026

35 Société Française de Pédiatrie. Recommandations. https://www.sfpediatrie.com/ressources/recommandations.

36 Flannery DD, Akinboyo IC, Mukhopadhyay S *et al*. Antibiotic susceptibility of *Escherichia coli* among infants admitted to neonatal intensive care units across the US from 2009 to 2017. *JAMA Pediatr* 2021; **175**: 168–75. https://doi.org/10.1001/jamapediatrics.2020.4719

37 Melzer M, Petersen I. Mortality following bacteraemic infection caused by extended spectrum beta-lactamase (ESBL) producing *E. coli* compared to non-ESBL producing *E. coli*. *J Infect* 2007; **55**: 254–9. https://doi.org/10.1016/j.jinf.2007.04.007

38 Chu S-M, Hsu J-F, Lai M-Y *et al*. Risk factors of initial inappropriate antibiotic therapy and the impacts on outcomes of neonates with Gram-negative bacteremia. *Antibiotics (Basel)* 2020; **9**: E203. https://doi.org/10.3390/antibiotics9040203