

Escherichia Coli Meningitis Features in 325 Children From 2001 to 2013 in France

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Background. We aimed to describe features of *Escherichia coli* meningitis in a large population of children and the molecular characteristics of the involved strains to determine factors associated with severe disease or death.

Methods. Between 2001 and 2013, a prospective national survey collected data for 325 children hospitalized with *E. coli* meningitis. The national reference center genetically characterized 141 isolates.

Results. Among the 325 cases, 65.2% were term, 22.4% late preterm, and 12.5% very/extremely preterm infants. *Escherichia coli* meningitis was 7-fold more frequent in preterm than term infants. Median age at diagnosis was 14 days; 71.1% of infants were neonates, with 2 peaks of infection at age 0–3 days (mostly preterm neonates) and 11–15 days (mostly term neonates); 8.9% were >89 days old. In total, 51.1% patients were considered to have severe disease, and 9.2% died. B2.1 phylogenetic subgroup (56%) and O1 serogroup (27.7%) were the most frequently identified. On multivariate analysis, death was associated with preterm birth (odds ratio [OR], 3.3 [95% confidence interval {CI}, 1.3–8.4], $P = .015$ for late preterm infants; OR, 7.3 [95% CI, 2.7–20.9], $P < .001$ for very/extremely preterm infants) and cerebrospinal fluid (CSF) to blood glucose ratio <0.10 (OR, 15.3 [95% CI, 1.8–128.3], $P = .012$). Death was associated with uncommon O serogroup strains ($P = .014$) and severe disease with O7 serogroup ($P = .034$) and PapGII adhesin (OR, 2.3 [95% CI, 1.2–4.5], $P = .015$).

Conclusions. In this large study of 325 cases of *E. coli* meningitis, risk factors of severe disease or death were preterm birth, severe hypoglycemia, CSF/blood glucose ratio <0.10 , and molecular characteristics of strains, which should help optimize therapeutic management.

Keywords. *Escherichia coli*; meningitis; children; neonatal infection.

Bacterial meningitis is associated with high mortality and morbidity, reaching 15% and 50%, respectively, especially during the neonatal period [1–5]. *Escherichia coli* is the first cause of bacterial meningitis in preterm infants and the second cause after group B streptococci in term infants [1, 5, 6]. In France between 2001 and

2013, the mean number of births per year was 814 000, almost 6.6% being preterm [7]. Neonates (≤ 28 days) are the population at greatest risk for *E. coli* meningitis. However, *E. coli* meningitis may occur in older infants, even when excluding cases of immunodeficiency or neurosurgical cause [8–11].

Several international studies provided the genetic characterization of *E. coli* meningitis strains including phylogenetic groups and virulence determinants [2, 12–16]. However, we lack an association between these strain characteristics and disease severity or mortality rates, and the risk factors of severe *E. coli* meningitis remain to be elucidated [2, 17].

In 2001, the Pediatric Infectious Diseases Group of the French Pediatric Society (GPIP/ACTIV) established

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an active bacterial pediatric meningitis surveillance network in representative hospital sites to collect the features of bacterial meningitis [9, 18]. Moreover, the *E. coli* national reference center collected data on and genetically characterized the strains isolated.

We analyzed *E. coli* meningitis severity and mortality by characteristics of patients as well as genetic characteristics of the strains.

PATIENTS AND METHODS

Between 2001 and 2013, 233 pediatric wards and 168 microbiology laboratories participated in this French national survey. All patients <18 years old with confirmed *E. coli* meningitis were included in the study.

A standardized form was completed on site by a designated clinical investigator and was sent by electronic or postal mail to the investigating center (ACTIV). Three times a year, each clinical investigator from each participating ward was contacted to declare bacterial meningitis cases or to confirm their absence. The capture–recapture method for meningitis was previously used to evaluate the completeness of the system, at 61% (95% confidence interval [95% CI], 60%–66%) [19]. The data covered by the standardized form were previously detailed [1]. The diagnosis of meningitis was based on positive culture of cerebrospinal fluid (CSF), and/or positive direct examination of CSF, and/or presence of positive soluble antigens in CSF, and/or positive polymerase chain reaction (PCR) results for CSF, and/or positive blood culture associated with pleocytosis (≥ 10 cells/ μL) in CSF [1]. At diagnosis, disease severity criteria were coma, mechanical ventilation, shock, seizures, and extensive purpura. Short-term outcomes were recorded as type of complication (eg, seizures, empyema, cerebral abscess, stroke, death). Patients presenting at least 1 criterion among the initial severity criteria and/or early complication were considered to have severe disease.

Initially, local microbiology laboratories performed bacterial isolate identification, K1 capsular antigen determination, and amoxicillin and third-generation cephalosporin (3GC) susceptibility determination, as recommended by the French Microbiology Society [20]. Second, these laboratories were encouraged to report the strains to the *E. coli* national reference center for phylogenetic grouping and detection of *E. coli* genetic factors, as previously described [21]. Eight common O serogroups were determined; others were considered uncommon O serogroups, and 9 virulence genes were searched for (Table 1). A virulence score was calculated as 1 point for the presence of each virulence determinant (K1 antigen and virulence genes), with the total score ranging from 0 to 10.

We cross-checked the databases of the *E. coli* national reference center and ACTIV to analyze meningitis severity and/or mortality rates and correlated them with genetic characteristics of strains. Clinical characteristics of some of this population were previously published [1].

Ethical Approval

The data collection was approved by the French National Data Protection Commission (number 913006).

Statistical Analysis

Continuous variables were compared by Mann–Whitney *U* test or Student *t* test. Categorical variables were compared by Fisher exact test. Clinical and biological variables identified on univariate analysis ($P < .20$) as potential factors associated with severity or death were introduced in multivariate logistic regression models to estimate odds ratios (ORs) and 95% CIs. Missing data were taken into account. Because of few cases in each “O serogroup” subclass, only univariate analysis was performed. Independent of clinical and biological data, the results for the virulence genes potentially associated with disease severity on univariate analysis ($P < .20$) were included in a second multivariate analysis model. All analyses involved use of R version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria). A *P* value $< .05$ was considered statistically significant.

RESULTS

Demographic, Clinical, and Biological Features of *E. coli* Meningitis

Between 2001 and 2013, data for 5567 cases of bacterial meningitis were collected; 328 (5.9%) were due to *E. coli* and distributed among 126 pediatric wards. Three hundred twenty-five cases in total were included: 283 *E. coli*-positive CSF cultures, 13 positive CSF Gram staining (gram-negative rod), 5 positive K1 capsular antigens, 1 positive PCR result, and 23 CSF pleocytosis ≥ 10 cells/ μL with positive blood culture. Three cases with pleocytosis ≥ 10 cells/ μL and positive gastric culture at birth were excluded. The number of *E. coli* meningitis cases was 19–33 per year during the study period, with no significant trends (Figure 1). The global incidence of *E. coli* meningitis was estimated at 5.3 per 100 000 births: 3.8 per 100 000 and 26 per 100 000 for term and preterm births, respectively. Therefore, *E. coli* meningitis appeared to be 7-fold more frequent in preterm than term infants.

Demographic characteristics of the 325 cases are shown in Table 1. The median age of patients was 14 days; 231 (71.1%) were newborn, 65 (20.0%) 29–89 days old, and 29 (8.9%) >89 days old (Figure 2). The age at meningitis development was significantly younger for very/extremely preterm and late preterm infants than for term infants (Table 1 and Figure 2). We observed 2 peaks of disease prevalence by age: the first between age 0 and 3 days ($n = 66$), corresponding to early-onset meningitis, and the second between age 11 and 15 days ($n = 64$) (Figure 2). Term infants represented 27 of 65 (40.9%) of the 0- to 3-day-old group and 49 of 60 (81.7%) of the 11- to 15-day-old group ($P < .001$). Among the 29 infants >89 days old, 2 had

Table 1. Characteristics of Cases of *Escherichia coli* Meningitis and Strains by Gestational Age of Children in France, 2001–2013

Characteristics	All Cases	Very/Extremely Preterm Infants	Late Preterm Infants	Term Infants
Patients	325	39 (12.5)	70 (22.4)	204 (65.2)
Demographic data				
Male/female (ratio)	179/138 (1.30)	21/16 (1.31)	37/31 (1.19)	114/86 (1.33)
Initial presentation				
Age, d, median (10th–90th percentile)	14 (1–82)	9 (0–81)*	7 (0–45)**	15 (3–94)
At least 1 sign of severity ^a	123 (37.8)	26 (66.7)**	45 (64.3)**	48 (23.5)
Blood culture ^b	210/66 (76.1)	29/5 (85.3)***	52/11 (82.5)***	120/49 (71.0)
CSF/blood glucose ratio <0.50 ^b	139/39 (78.1)	17/2 (89.5)	30/9 (76.9)	88/27 (76.5)
Outcome				
Any complication but death ^b	78/217 (26.4)	5/24 (17.2)	18/42 (30)	52/142 (26.8)
Died	30 (9.2)	9 (23.1)**	10 (14.3)*	10 (4.9)
Severe disease ^c	166 (51.1)	29 (74.4)**	51 (72.9)**	81 (39.7)
Strains	141	13	28	94
<i>E. coli</i> phylogenetic group or subgroup				
A	7 (5.0)	0 (0.0)	2 (7.1)	3 (3.2)
B2 (not B2.1)	31 (22.0)	3 (23.1)	6 (21.4)	20 (21.3)
B2.1	79 (56.0)	7 (53.8)	14 (50.0)	56 (59.6)
D	24 (17.0)	3 (23.1)	6 (21.4)	15 (16.0)
O serogroup				
O1	39 (27.7)	2 (15.4)	7 (25.0)	29 (30.9)
O18	27 (19.1)	2 (15.4)	6 (21.4)	18 (19.1)
O45	16 (11.3)	2 (15.4)	2 (7.1)	12 (12.8)
O7	9 (6.4)	1 (7.7)	3 (10.7)	5 (5.3)
O2	5 (3.5)	5 (5.3)
O6	4 (2.8)	1 (7.7)	2 (7.1)	1 (1.1)
O16	4 (2.8)		1 (3.6)	3 (3.2)
O83	3 (2.1)			3 (3.2)
Uncommon ^d	34 (24.1)	5 (38.5)	7 (25.0)	18 (19.1)
Virulence determinants ^{b,e}				
K1 antigen ^f	207/42 (83.1)	22/6 (78.6)	41/9 (82.0)	139/23 (85.8)
<i>iucC</i>	124/17 (87.9)	10/3 (76.9)	25/3 (89.3)	86/11 (88.65)
<i>cnf1</i>	8/133 (5.7)	1/12 (7.7)	3/25 (10.7)	3/94 (3.09)
<i>fyuA</i>	136/3 (97.8)	11/1 (91.7)	28/0 (100)	94/2 (97.91)
<i>hlyC</i>	15/126 (10.6)	1/12 (7.7)	4/24 (16.7)	8/89 (8.24)
<i>hlyA/hek</i>	14/122 (11.1)	1/11 (8.3)	5/18 (21.3)	7/82 (7.86)
<i>ibeA</i>	47/94 (33.6)	6/7 (46.2)	8/20 (28.6)	32/64 (33.33)
<i>iroN</i>	106/35 (75.2)	10/3 (76.9)	19/9 (67.9)	75/22 (77.31)
<i>papGII</i>	71/70 (50.4)	6/7 (46.2)	16/12 (57.1)	48/49 (49.48)
<i>papGIII</i>	3/138 (2.1)	0/13 (0)	1/27 (3.6)	2/95 (2.06)
<i>sfa/foc</i>	36/105 (25.5)	4/9 (30.8)	8/20 (28.6)	23/74 (23.71)
Virulence score, median (10th–90th percentile); mean	5 (3–6); 4.84	5 (3–6); 4.77	5 (3–6.3); 4.96	5 (3–6); 4.83
Susceptible/resistant to amoxicillin ^f	149/118 (55.8)	14/14 (50.0)	32/25 (56.1)	101/71 (58.7)

Data are presented as No. (%) unless otherwise indicated. Very/extremely preterm, gestational age (GA) <32 weeks; late preterm, GA 32–36 weeks + 6 days; term, GA ≥37 weeks.

Results with significant differences are indicated in boldface.

Abbreviation: CSF, cerebrospinal fluid.

^a Severity at diagnosis: coma, mechanical ventilation, shock, seizure, extensive purpura.

^b Data are shown as positive/negative (%).

^c Severe: any sign of disease severity at diagnosis and/or any early complication and/or death.

^d Uncommon O serogroups were O5, O8, O14, O21, O23, O77, O78, and O not typeable.

^e The virulence genes detected were iron-uptake systems (*fyuA*, yersiniabactin; *iroN*, salmochelin; *iucC*, aerobactin), hemolysin (*hlyC*), S fimbriae adhesins (*sfa/foc*) and P fimbriae adhesins (*papGII* and *papGIII*), endothelial invasin (*ibeA*), cytotoxin necrotizing factor CNF1 (*cnf1*), and hemagglutinin (*hlyA/hek*).

^f K1 antigen determination and amoxicillin susceptibility testing for 249 and 267 strains, respectively, were performed by local laboratories.

* $P = .02$.

** $P < .001$ vs term infants.

*** Very/extremely and late preterm infants pooled, $P = .03$ vs term infants.

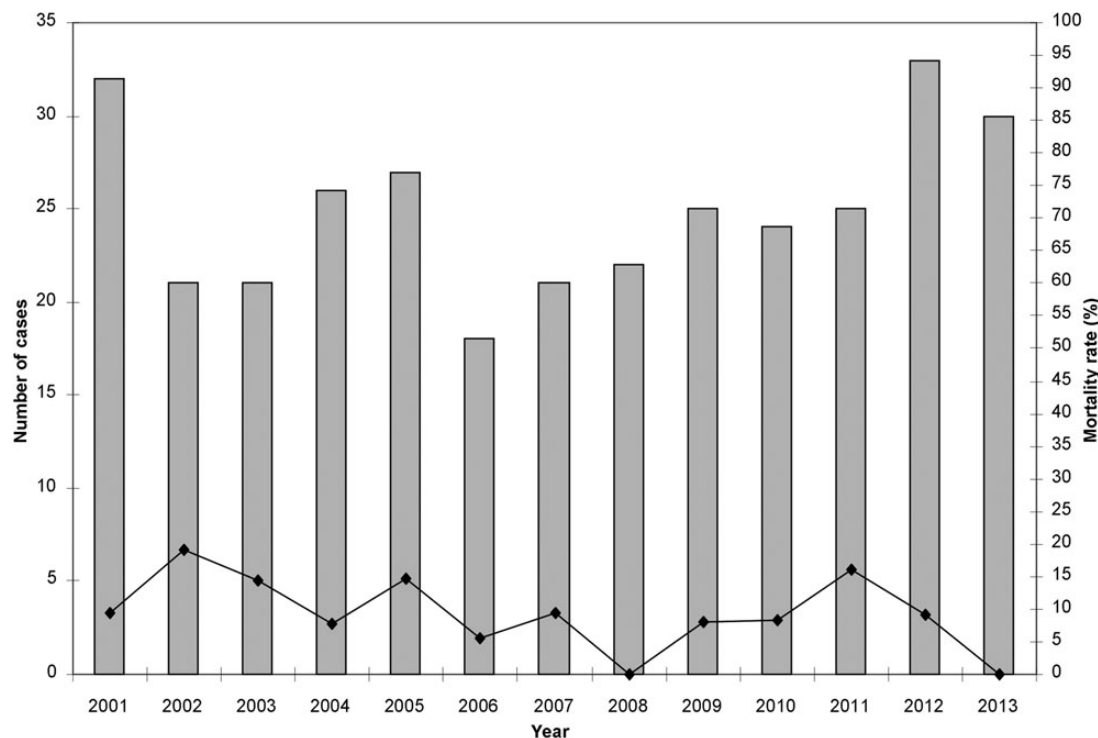


Figure 1. Cases of *Escherichia coli* meningitis (bars) in children and mortality (line) per year in France, 2001–2013.

recurrent meningitis (1 with meningeal breach), and 1 had ventricular derivation; however, no risk factor was mentioned for the 26 other patients.

At diagnosis, 123 patients (37.8%) presented at least 1 sign of disease severity; 93 needed mechanical ventilation (28.6%), 59 showed signs of shock (18.2%), 35 were in a coma (10.8%), 24 had seizures (7.4%), and 2 presented extensive purpura (0.6%). Signs of disease severity were more frequent for very/extremely preterm and late preterm than term infants at diagnosis (66.7% and 64.3% vs 23.5%, respectively; $P < .001$; Table 1).

The median white blood cell count at diagnosis, available for 204 children, was 7930 cells/ μ L (10th–90th percentile, 1900–20 912 cells/ μ L), with no significant differences between very/extremely preterm, late preterm, and term children. Blood cultures were more frequently positive for preterm than term children (81/97 [83.5%] vs 120/169 [71.0%], respectively; $P = .03$; Table 1). For 300 cases, characteristics of CSF were available: Median pleocytosis was 2300 cells/ μ L (10th–90th percentile, 50–14 040 cells/ μ L) with 85% neutrophils (10th–90th percentile, 54%–97.1%), and the median protein value 2.26 g/L (10th–90th percentile, 0.73–7.21 g/L). The CSF/blood glucose ratio was available for 178 cases: 139 (78.1%) had a hypoglycorrhachia ratio <0.50 , including 75 (42.1%) with a ratio <0.10 . Of note, 15 children (5.0%) aged 0–52 days (5 were >28 days old) presented no CSF pleocytosis (<10 cells/ μ L), and all had *E. coli*-positive CSF culture.

Treatment and Evolution

Antibiotic therapy contained a 3GC (mostly cefotaxime, median dose 200 mg/kg/day) for 316 cases (96.9%). For 249 cases with available data, after excluding dead patients, the median duration of 3GC treatment was 20 days. Ciprofloxacin was added for 157 cases (48.3%).

In total, 108 patients (33.2%) experienced at least 1 complication; 30 died (30/325 [9.2%]). The mortality rate per year ranged from 0.0% to 19.0% (Figure 1), with no significant trends, but was 3.5-fold higher for preterm than term infants (19/109 [17.4%] vs 10/204 [4.9%], respectively; $P < .001$; Table 1). The most frequent complications were seizures ($n = 42$ [12.9%]; 28 term, 13 preterm and 1 unknown term infants; $P = .16$), followed by empyema ($n = 19$ [5.8%]; 12 term, 6 preterm and 1 unknown infants, $P = .60$), followed by empyema ($n = 19$ [5.8%]; 12 term and 6 preterm infants, $P = .60$), intraventricular bleeding, hydrocephaly, or intracranial hypertension ($n = 16$ [4.9%]), cerebral thrombophlebitis or stroke ($n = 10$ [3.1%]), ventriculitis or pachymeningitis ($n = 6$ [1.8%]), shock ($n = 6$ [1.8%]), cerebral abscess ($n = 4$ [1.2%]), and nosocomial infections ($n = 1$ [0.3%]). Six patients (1.8%) showed disease relapse despite appropriate antibiotic treatment.

A second lumbar puncture was performed 48 hours after treatment initiation for 244 cases (244/310 [78.7%]); results were available for 235 and the culture remained positive for 32 (32/235 [13.6%]). For these cases, the median duration of

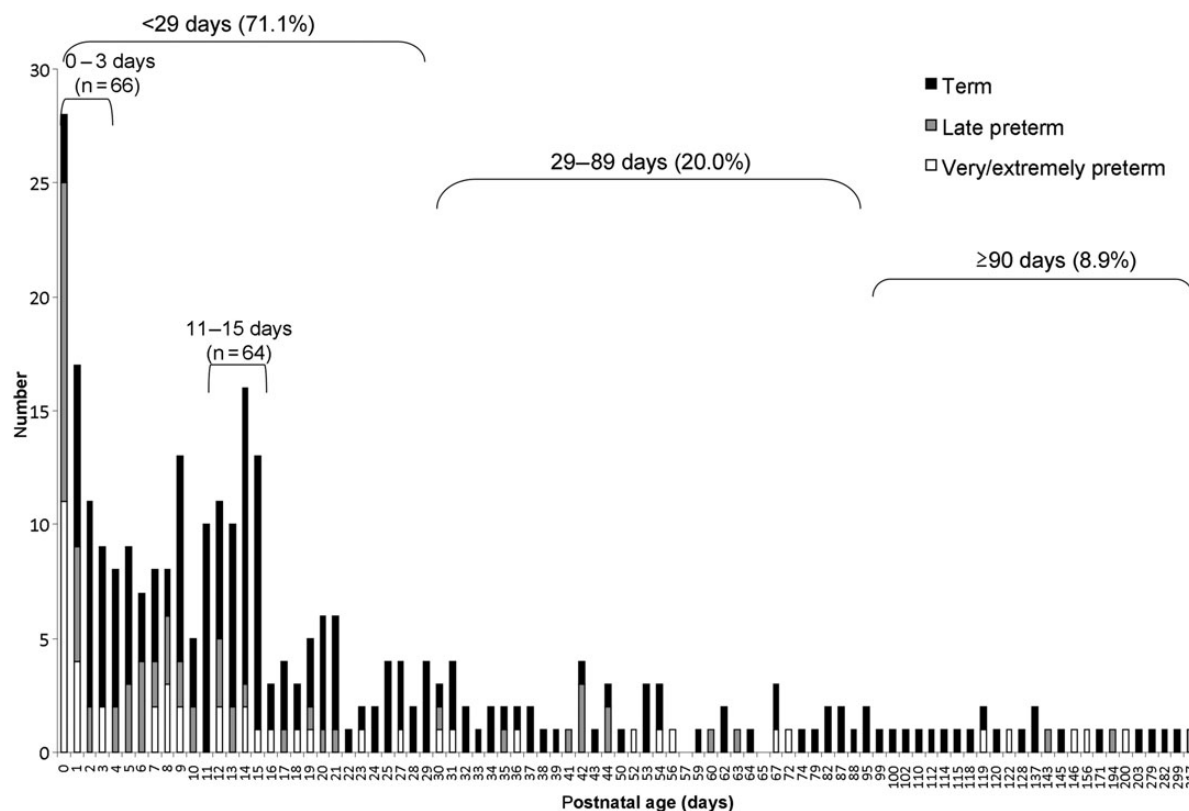


Figure 2. Cases of *Escherichia coli* meningitis by age at diagnosis (postnatal days). Only ages with at least 1 case are shown on the x-axis. Term, gestational age (GA) ≥ 37 weeks; late preterm, GA 32–36 weeks + 6 days; and very/extremely preterm, GA < 32 weeks.

3GC treatment was 21 days; 14 (43.8%) experienced at least 1 complication, except death, compared with 53 of 203 (26.1%) with a sterile second lumbar puncture ($P = .056$), and 3 additional patients died (9.4%).

Microbiological and Genetic Characteristics of Isolated Strains

For the 325 cases with *E. coli* meningitis, local laboratories performed K1 capsular antigen detection for 249 strains (76.6%), and 207 (83.1%) were positive, with no significant difference by gestational age (Table 1).

For the 325 cases, 141 (43.4%) strains were sent to the *E. coli* national reference center and were further genetically characterized. Cases with or without an available strain did not differ (Supplementary Table 1). Serogroup O1 was the predominant O serogroup (39/141 [27.7%]), followed by O18 (27/141 [19.1%]), O45 (16/141 [11.3%]), and O7 (9/141 [6.4%]) (Table 1). Of note, the prevalence of O45 decreased after 2004, but other major O serogroups were stable over the years.

Phylogenetic group analysis revealed 7 strains belonging to group A (5.0%), 110 to group B2 (78%), 79 to subgroup B2.1 (56.0%), and 24 to group D (17.0%). No strain belonged to group B1.

Results of PCR assay of virulence genes for the 141 strains are shown in Table 1. More than 75% of the 141 studied isolates

showed expression of the iron-uptake system genes *fyuA* (yersiniabactin), *iucC* (aerobactin), and *iroN* (salmochelin), whereas expression of other extraintestinal pathogenic factors such as *hlyA/hek*, *hlyC*, *papGIII*, and *cnf1* was rare ($< 15\%$). Prevalence of virulence genes did not differ by gestational age group (Table 1).

Local laboratories performed amoxicillin susceptibility tests for 267 strains: 118 (44.2%) were not susceptible, and 4 (1.5%) produced extended-spectrum β -lactamase (1 in 2005, 1 in 2008, and 2 in 2010). The rate of amoxicillin resistance appeared to be stable over the years, especially between the 2 periods before and after the implementation of intrapartum maternal antibiotic prophylaxis against group B streptococci: 2001–2002 and 2003–2013 (median rates of 37.7% and 43.8%, respectively; $P = .11$).

Risk Factors of Severity and Mortality of *E. coli* Meningitis

On comparing the 166 patients with severe disease and 159 with nonsevere disease, univariate analysis revealed that severe disease was associated with preterm birth, with more positive blood culture and with a CSF/blood glucose ratio < 0.10 . Similarly, patients who died ($n = 30$) were younger and more often exhibited preterm births than survivors ($n = 290$); CSF/blood glucose ratio was more frequently < 0.10 (Supplementary Table 2).

Table 2. Multivariate Logistic Regression Assessment of Risk Factors of Severe Disease and Death in Cases of Children With *Escherichia coli* Meningitis

Factor	Severe Disease		Death	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Model 1: Clinical and biological data				
Term infants	1		1	
Late preterm infants	4.1 (2.2–7.4)	<.001	3.3 (1.3–8.4)	.015
Very/extremely preterm infants	4.4 (2.0–9.5)	<.001	7.3 (2.7–20.9)	<.001
CSF/blood glucose ratio				
0.10–0.50			1	
<0.10			15.3 (1.8–128.3)	.012
Model 2: Virulence genes				
Other	1			
<i>papGII</i>	2.3 (1.2–4.5)	.015		

Severe disease included presence of any sign of severe disease at initial presentation and/or any early complication and/or death.

Abbreviations: CI, confidence interval; CSF, cerebrospinal fluid; OR, odds ratio.

On multivariate logistic regression, preterm birth was the only independent factor associated with disease severity ($P < .001$), whereas preterm birth and severe hypoglycorrhachia (CSF to blood glucose ratio <0.10) were both independent risk factors of death ($P < .02$) (Table 2).

We performed a separate analysis to determine whether several bacterial characteristics were associated with disease severity or death for the strains sent to the national reference center. Univariate analysis revealed that O7 serogroup and PapGII adhesin increased the risk of disease severity ($P < .05$), but *sfa/foc* expression decreased the risk ($P = .034$) (Supplementary Table 2). On multivariate logistic regression, PapGII adhesin was independently associated with disease severity (Table 2). Considering death, only uncommon O serogroups appeared to be significantly positively associated ($P = .014$) (Supplementary Table 2).

DISCUSSION

To our knowledge, this study is the largest describing *E. coli* meningitis cases to date, including 325 children during a 13-year period in France. The number of reported *E. coli* meningitis was stable during the study period, with 25 ± 4.6 cases per year. The global incidence of *E. coli* meningitis was 5.3 per 100 000, which is close to that recently published by Okike et al for the United Kingdom and Republic of Ireland (ie, 4/100 000) [5]. In our study, the mean mortality rate was 9.2% and was about 2 times higher in preterm and 2 times lower in

term infants. Even if we found no trend in mortality rate during the years, the rate appeared to be lower than that observed in previous studies, previously described to be 19%–26% before 1990 [8, 22, 23] and about 15% in more recent studies [5, 6]. This difference may be associated with improved management of severe disease, despite the high rate of severe initial presentation (37.8%) and a high rate of complications (33.2%).

Escherichia coli meningitis is a complication of *E. coli* bacteremia during the neonatal period, and most epidemiologic studies are limited to this age period (ie, <29 days) [1, 4, 22]. Here, we showed that more than one-quarter of the meningitis cases occurred in children aged >28 days and 8.9% in those aged >89 days. Of note, the precise description of the age distribution allowed us to reveal 2 high-risk periods of *E. coli* meningitis development: 0–3 days old, associated with preterm neonates; and 11–15 days old, associated with term neonates. To our knowledge, this double-peak distribution has not been previously described. Although two-thirds of *E. coli* meningitis cases occurred in term infants, the incidence was 7-fold higher in preterm than term infants.

Although the diagnosis was mostly by positive CSF culture (87.1%), we observed a higher sensitivity of blood culture during *E. coli* meningitis (76.1%) than that observed in bacterial meningitis by Okike et al (68.1%) and Garges et al (62%) [5, 24]. The even higher rate of positive blood culture ($>80\%$) that we observed in preterm infants and severe cases strengthens the usefulness of cultures in these cases, for which testing with lumbar puncture could fail or be delayed. Moreover, positive blood culture allowed for bacterial identification in 23 cases (7.1%), with pleocytosis in sterile CSF. However, CSF parameters must be interpreted with caution, because 5% of CSF samples with *E. coli*-positive culture contained <10 cells/ μL at diagnosis and 21.9% showed normal glycorrachia.

Of interest, despite 3GC treatment, CSF cultures remained positive for 13.6% of cases, which showed more complications, although not significantly, than those with sterile second CSF samples. In addition to increased permanent neurologic sequelae described in gram-negative meningitis with persistent positive CSF culture after 48 hours [8], our results suggest that caution must be taken for these cases, and antibiotic treatment should be continued at least for the recommended 21 days [25].

In our study, mortality was higher for preterm than other infants, which was not described by Unhanand et al [8], but appeared consistent with a recent study describing higher mortality for preterm (17%) than term neonates (4%) among children <90 days old [5]. Moreover, we confirmed a low CSF to glucose ratio (<0.50) to be associated with disease severity [8], but also highlighted that a severe hypoglycorrhachia CSF/blood glucose ratio (<0.10) was strongly and independently associated with mortality.

We genetically characterized the largest number of isolates described to date, representative of the *E. coli* meningitis cases in France. The O18 serogroup was previously described as the predominant serogroup in *E. coli* meningitis strains worldwide [2, 14, 26, 27], and an O45-like serogroup had emerged in France [28], but we observed that the O1 serogroup became predominant among our cases in France. Whether this predominance is associated with the emergence of a particular clone remains to be determined. Uncommon O serogroup was the unique bacterial characteristic associated with death. Despite a high propensity to cause death, these uncommon O serogroups possess fewer virulence factors than common O serogroups (mean virulence score of 3.94 and 5.13, respectively; $P < .001$). Although we observed only a trend in our study, Houdouin et al previously found these uncommon O serogroups to be significantly frequent in preterm infants [2]. Because we did not observe significant differences in virulence score by gestational age, disease severity, or mortality, apart from an accumulation of virulence factors, an altered balance between host defences and *E. coli* virulence may be involved in bacterial meningitis severity.

Moreover, we highlight for the first time the association of O7 serogroup and PapGII adhesin with severe meningitis. The O7 serogroup is frequently associated with *E. coli* meningitis and is intercontinentally distributed [27], whereas PapGII adhesin is associated with upper urinary tract infections [27], corresponding to a portal of entry that was recently described as not associated with severe *E. coli* bacteremia in infants [17]. Unfortunately, the population survey does not allow for determining whether meningitis was associated with urinary tract infections.

Finally, analysis of amoxicillin susceptibility over the years revealed a strong stability of the resistance prevalence (around 45%), despite high antibiotic consumption in France and implementation of intrapartum maternal antibiotic prophylaxis against group B streptococci since 2002 [29, 30]. The rate of amoxicillin resistance we observed appeared lower than that described in France in a recent study [31]: 61.6% of 2284 *E. coli* strains, isolated from 2004 to 2014, were resistant to ampicillin. We observed only 4 cases producing an extended-spectrum β -lactamase, so the first-line antibiotic treatment should not be modified yet.

In conclusion, we describe the largest population of *E. coli* meningitis published to date. Although *E. coli* meningitis is the first cause of bacterial meningitis in preterm neonates, with a 7-fold higher incidence than in other neonates, two-thirds of cases occurred in term infants and one-quarter occurred after the neonatal period. We observed 2 high-risk periods: age 0–3 days, mostly concerning preterm neonates, and age 11–15 days. Mortality rate was <10% and probably decreased over the years, despite high rates of initial severe presentation and early complications. Independent risk factors of severe disease or mortality, such as preterm birth, severe hypoglycorrhachia, CSF to blood glucose ratio <0.10, and

molecular characteristics of strains, should help optimize the therapeutic management. We observed changes in the epidemiology of O serogroups compared with previous studies, which emphasizes the importance of surveillance to detect new clones that could be more virulent or more resistant than current ones.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (<http://cid.oxfordjournals.org>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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