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Early-onset neonatal sepsis in the Paris area: a population-based surveillance study from 2019 to 2021

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ABSTRACT

Background Early-onset neonatal sepsis (EOS) is a rare condition but an important cause of severe morbidity and mortality in neonates.

Methods This is a prospective observational study in neonates born at ≥ 34 weeks of gestation (WG). The primary endpoint was EOS, defined by isolation of pathogenic species from blood culture and/or cerebrospinal fluid culture within 72 hours after birth. Data on EOS were collected exhaustively from all maternity wards in Paris area (April 2019–March 2021).

Results 108 EOS were recorded (annual incidence, 0.32 per 1000 live births; 95% CI 0.26 to 0.38). In term infants, the most frequent pathogens were group B *Streptococcus* (GBS) (n=47) and *Escherichia coli* (n=20); in late preterm infants, the most frequent pathogens were *E. coli* (n=15) and GBS (n=7). Fifteen meningitis cases were diagnosed. Five *E. coli* strains (14%) were resistant to both amoxicillin and gentamicin, which is an empiric treatment for EOS. Of the 54 infants with GBS infections, 35 were born from mothers with negative GBS prepartum screening test and 8 from mothers with no screening. Two deaths were reported, both in term infants (*Proteus mirabilis* and *E. coli*).

Conclusion In neonates ≥ 34 WG born in the Paris area, GBS was twice as frequent as *E. coli* in term infants. EOS was six times more frequent in late preterm than in term infants and was due to *E. coli* in 60% of cases. Prevention of GBS EOS and empiric antibiotic treatment of EOS could be improved.

INTRODUCTION

Early-onset neonatal sepsis (EOS) has a low incidence in developed countries but has potentially serious consequences. The incidence of EOS within 72 hours after birth regardless of term was estimated between 0.7 and 1.1 per 1000 live births in the USA.^{1–4} Mortality varies according to the gestational age of the newborn, from 2% to 3% in term infants to more than 20% in preterm infants,² and is even higher in cases of meningitis, at 10% and 26%, respectively.⁵ In developed countries, EOS in term and near-term infants is mainly due to group B *Streptococcus* (GBS) (40%–50% of cases) and *Escherichia coli* (10%–20%).^{1 2 6 7} Although GBS is the most common pathogen, mortality is most frequently due to *E. coli*.^{3 8}

There is no national EOS register in France. Since 2011, only the incidence of early neonatal GBS infections has been reported and was estimated to be

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Early-onset neonatal sepsis (EOS) has a low incidence in developed countries but has potentially serious consequences.
- ⇒ In France, prevention of EOS due to group B *Streptococcus* (GBS) is mainly based on antepartum GBS screening test.
- ⇒ The French Society of Neonatology published guidelines in 2017 for EOS in neonates ≥ 34 weeks of gestation; epidemiological and management data on EOS should be updated.

WHAT THIS STUDY ADDS

- ⇒ The annual incidence of EOS was 0.32 per 1000 live births and was six times more frequent in late preterm than in term infants.
- ⇒ Eleven newborns (10.2%) remained asymptomatic (seven of them were born in chorioamnionitis background), indicating that clinical examination alone may not be sufficient for EOS diagnosis.
- ⇒ 68.6% of 35 strains of *Escherichia coli* were resistant to amoxicillin and 14.3% were resistant to both amoxicillin and gentamicin.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ Our results encourage the use of peripartum sensitive GBS screening test using PCR.
- ⇒ Close monitoring of *E. coli* aminoglycoside resistance is essential to adapt empiric antibiotic treatment in infants with suspected sepsis whose mothers received adequate antibiotic prophylaxis for GBS infection.

~0.20 per 1000 live births by the French network EPIBAC.⁹ Proven EOS is rare, but suspicion of EOS is fairly common in daily practice. Previous studies showed that more than half of neonates in France had a gastric aspirate at birth,^{10–12} which may have led to unnecessary complementary examinations, and 4% of infants received antibiotic treatment for suspected EOS.¹² The French Society of Neonatology and the French Society of Pediatrics have updated in 2017 the guidelines for EOS in neonates ≥ 34 weeks of gestation (WG).¹³ Briefly, symptomatic newborns are treated empirically with antibiotics, and for asymptomatic newborns a categorical approach based on peripartum risk factors and intrapartum antibiotics identifies those who require



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Table 1 Annual incidence of early-onset neonatal sepsis in the Paris area in late preterm (34–36 WG) and term (≥ 37 WG) infants

Pathogens	Cases per 1000 births (n)		
	All study infants	Late preterm (34–36 WG)	Term (≥ 37 WG)
Group B <i>Streptococcus</i>	0.16 (0.12 to 0.21)	0.42 (0.20 to 0.86)	0.15 (0.11 to 0.19)
<i>Escherichia coli</i>	0.10 (0.07 to 0.14)	0.89 (0.54 to 1.47)	0.06 (0.04 to 0.10)
Others	0.06 (0.04 to 0.09)	0.18 (0.06 to 0.53)	0.05 (0.03 to 0.08)
Total	0.32 (0.26 to 0.38)	1.49 (1.01 to 2.20)	0.26 (0.21 to 0.32)

Results are given as annual incidence with Wilson's 95% CI. WG, weeks of gestation.

serial clinical monitoring every 4 hours through 48 hours of age. Two years after the release of the new recommendations, the creation of an observatory in the Paris area appeared necessary. The primary objective was to estimate the annual incidence and pathogen distribution in EOS. The secondary objective was to describe the clinical characteristics of mothers and infants and their management.

MATERIALS AND METHODS

Study design and patients

This was an exhaustive, prospective, observational, multicentre study (from 1 April 2019 to 31 March 2021) of EOS in neonates born at 34 WG in the Paris area (formally, Île-de-France region). The Paris area is the largest region in France (14 million inhabitants in 2021) and the largest urban region in the European Union. The Paris area had 81 maternity wards at the beginning of the study, 3 of which closed in 2020.

EOS was defined as a positive blood culture and/or cerebrospinal fluid culture to a pathogen within 72 hours after birth. Infants were excluded when the organism was a contamination such as coagulase-negative staphylococci, *Micrococcus*, *Bacillus*, *Corynebacterium* and *Propionibacterium* species, or if sepsis was

secondary to another infection or a particular disease such as enterocolitis in Hirschsprung's disease.

Recruitment took place at the time of diagnosis, after families received information and agreed to participate. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Data collection

A weekly reminder email was sent to all neonatologists and bacteriologists in the Paris area to report each EOS. The following data were recorded by a senior paediatrician: infant and maternal demographics, maternal risk factors, maternal antibiotic therapy peripartum, notably GBS antibiotic prophylaxis (adequate: penicillin, ampicillin or cefazolin administered at least 4 hours before delivery; inadequate in other cases) or antibiotic therapy within 72 hours of delivery, newborn clinical signs, C reactive protein, blood culture, cerebrospinal fluid culture, antibiotic therapy of infants and the outcomes, and antibiotic resistance of GBS and *E. coli* strains. When lumbar puncture was performed after starting antibiotic therapy, a positive bacterial PCR in the cerebrospinal fluid allowed to retain the diagnosis of meningitis.

Completeness of cases of bacterial infections was checked by recapturing the data from the bacteriologists associated with maternity wards (except for 5 out of 81). Five cases of EOS were retrieved from the computerised data of bacteriologists and were included in the study after consent of the parents.

Statistical analysis

Analyses were essentially descriptive and no formal hypotheses were tested. The primary outcome was the incidence rate, defined as the number of cases of EOS per 1000 births, with Wilson's 95% CI, diagnosed among live neonates ≥ 34 WG in all maternity wards in the Paris area. The total number of live births during this period was provided by the regional health agency

Table 2 Pathogens evidenced in blood and cerebrospinal fluid cultures according to the term of neonates

Pathogens	All study infants (N=108)		Late preterm (34–36 WG) (n=25)		Term (≥ 37 WG) (n=83)	
	Bacteraemia	Meningitis	Bacteraemia	Meningitis	Bacteraemia	Meningitis
Gram-positive	63 (58.9)	5 (33.3)	9 (36)	0	54 (65.9)	5 (50)
Group B <i>Streptococcus</i>	54 (50.5)	4 (26.7)	7 (28)	0	47 (57.3)	4 (40)
<i>Listeria monocytogenes</i>	5 (4.7)	1 (6.7)	2 (8)	0	3 (3.7)	1 (10)
<i>Streptococcus gallolyticus</i>	1 (0.9)	0	0	0	1 (1.2)	0
<i>Granulicatella adiacens</i>	1 (0.9)	0	0	0	1 (1.2)	0
<i>Streptococcus vestibularis</i>	1 (0.9)	0	0	0	1 (1.2)	0
<i>Enterococcus faecalis</i>	1 (0.9)	0	0	0	1 (1.2)	0
Gram-negative	44 (41.1)	10 (66.7)	16 (64)	5 (100)	28 (34.1)	5 (50)
<i>Escherichia coli</i>	35 (32.7)	8 (53.3)	15 (60)	5 (100)	20 (24.4)	3 (30)
<i>Klebsiella pneumoniae</i>	4 (3.7)	1 (6.7)	1 (4)	0	3 (3.7)	1 (10)
<i>Klebsiella oxytoca</i>	1 (0.9)	0	0	0	1 (1.2)	0
<i>Burkholderia cepacia</i>	1 (0.9)	0	0	0	1 (1.2)	0
<i>Campylobacter jejuni</i>	1 (0.9)	0	0	0	1 (1.2)	0
<i>Citrobacter koseri</i>	1 (0.9)	0	0	0	1 (1.2)	0
<i>Morganella morganii</i>	1 (0.9)	0	0	0	1 (1.2)	0
<i>Proteus mirabilis</i>	0	1 (6.7)	0	0	0	1 (10)
All cases*	107	15	25	5	82	10

Results are given as n (%).

*Total of 108 early-onset neonatal infections: 107 bacteraemia (including 14 with meningitis) and 1 meningitis without bacteraemia (*Proteus mirabilis*).

WG, weeks of gestation.

Table 3 Characteristics of infants and mothers at inclusion in the study and according to gestational age and pathogens

	All study infants				Late preterm (34–36 WG)			Term (≥ 37 WG)		
	Total (N=108)	GBS (n=54)	<i>E. coli</i> (n=35)	Total (n=25)	GBS (n=7)	<i>E. coli</i> (n=15)	Total (n=83)	GBS (n=47)	<i>E. coli</i> (n=20)	
Birth weight, g, mean (SD)										
≤2500	22 (20.4)	5 (9.3)	14 (40)	18 (72.0)	4 (57.1)	12 (80)	4 (4.8)	1 (2.1)	2 (10)	
>2500	86 (79.6)	49 (90.7)	21 (60)	7 (28.0)	3 (42.9)	3 (20)	79 (95.2)	46 (97.9)	18 (90)	
Apgar score ≥ 7 at 5 min, n (%)	90 (83.3)	48 (88.9)	29 (82.9)	23 (92.0)	7 (100)	14 (93.3)	67 (80.7)	41 (87.2)	15 (75)	
Method of delivery, n (%)										
Vaginal	83 (76.9)	45 (83.3)	27 (77.1)	19 (76.0)	6 (85.7)	11 (73.3)	64 (77.1)	39 (83.0)	16 (80)	
Caesarean section	25 (23.1)	9 (16.7)	8 (22.9)	6 (24.0)	1 (14.3)	4 (26.7)	19 (22.9)	8 (17.0)	4 (20)	
Mother's age, years										
Mean (SD)	30.6 (5.0)	30.3 (5.6)	31.3 (4.3)	32.2 (3.8)	32.6 (5.2)	31.7 (3.1)	30.1 (5.3)	30.0 (5.6)	30.9 (5.0)	
Range	18–42	18–42	20–40	25–40	25–40	26–38	18–42	18–42	20–40	
Antenatal risk factors, n (%)										
No GBS screening test	15 (13.9)	8 (14.8)	5 (14.3)	6 (24.0)	2 (28.2)	3 (20)	9 (10.8)	6 (12.8)	2 (10)	
GBS screening test* performed	93 (86.1)	46 (85.2)	30 (85.7)	19 (76.0)	5 (71.4)	12 (80)	74 (89.2)	41 (87.2)	18 (90)	
Positive	14 (15.1)	11 (23.9)	2 (6.7)	3 (15.8)	2 (40.0)	0	11 (14.9)	9 (22.0)	2 (11.1)	
Negative	79 (84.9)	35 (76.1)	28 (93.3)	16 (84.2)	3 (60.0)	12 (100)	63 (85.1)	32 (78.0)	16 (88.9)	
History of neonatal GBS infection	3 (2.8)	1 (1.9)	1 (2.9)	1 (4.0)	0	1 (6.7)	2 (2.4)	1 (2.1)	0	
Membrane rupture >12 hours	32 (29.6)	5 (9.3)	21 (60.0)	11 (44.0)	1 (14.3)	10 (66.7)	21 (25.3)	4 (8.5)	11 (55.0)	
Intrapartum maternal temperature >38°C	41 (38.0)	19 (35.2)	11 (31.4)	9 (36.0)	2 (28.6)	5 (33.3)	32 (38.6)	17 (36.2)	9 (30)	
No risk factors†	34 (31.5)	22 (40.7)	8 (22.9)	2 (8.0)	1 (14.3)	1 (6.7)	32 (38.6)	21 (44.7)	7 (35.0)	
No GBS screening test and no other risk factor	6 (5.6)	4 (7.4)	2 (5.7)	2 (8.0)	1 (14.3)	1 (6.7)	4 (4.8)	3 (6.4)	1 (5.0)	
Antibiotic treatment within 3 days before labour onset, n (%)	16 (14.8)	0	14 (40.0)	8 (32.0)	0	8 (53.3)	8 (9.6)	0	6 (30)	
Intrapartum antibiotic treatment, n (%)										
No antibiotic treatment	65 (60.2)	42 (77.8)	14 (40.0)	9 (36.0)	5 (71.4)	3 (20)	56 (67.5)	37 (78.7)	11 (55)	
Adequate treatment	26 (24.1)	0	20 (57.1)	13 (52.0)	0	12 (80)	13 (15.7)	0	8 (40)	
Inadequate treatment	17 (15.7)	12 (22.2)	1 (2.9)	3 (12.0)	2 (28.6)	0	14 (16.9)	10 (21.3)	1 (5)	

*Vaginal swab (PCR or or microbiological culture) and/or urine culture.

†Negative GBS screening test, no intrapartum maternal temperature >38°C, no membrane rupture >12 hours, no unexplained preterm birth and no history of neonatal GBS infection.

E. coli, *Escherichia coli*; GBS, group B *Streptococcus*; WG, weeks of gestation.

Table 4 Initial antibiotic treatment for early-onset neonatal sepsis and clinical evolution of infants

	All study infants (N=108)
Initiation of antibiotic treatment, n (%)	108 (100)
Time from birth to initiation of antibiotic treatment, n (%)	
<12 hours	62 (57.4)
≥12 hours	46 (42.6)
Initial antibiotic treatment, n (%)	
Amoxicillin–gentamicin	65 (60.2)
Amoxicillin–cefotaxime–gentamicin	21 (19.4)
Cefotaxime–gentamicin	14 (13.0)
Amoxicillin–cefotaxime–amikacin	2 (1.9)
Amoxicillin–amikacin	2 (1.9)
Cefotaxime–gentamicin–vancomycin	2 (1.9)
Cefotaxime–amikacin	1 (0.9)
Vancomycin–gentamicin	1 (0.9)
Modification of antibiotic treatment, n (%)	55 (50.9)
Duration of main antibiotic treatment, days, median (IQR)	
Sepsis	8 (7–10)
Sepsis plus meningitis	21 (21–21)
Transfer to another department, n (%)	101 (93.5)
Neonatal intensive care unit	73 (72.3)
Neonatology	28 (27.7)
Age (hours) at transfer, median	4.0
Death, n (%)	2 (1.9)

(Agence Régionale de Santé; ARS) of the Paris area and allowed calculation of annual incidence rates.

RESULTS

Incidence of early-onset sepsis

The study included 108 neonates born at ≥34 WG with a positive blood culture and/or cerebrospinal fluid culture to a bacterial pathogen within 72 hours after birth between 1 April 2019 and 31 March 2021. Among them, 83 were term infants (≥37 WG). During the 2-year study period, a total of 346 162 live births (gestational age ≥34 WG) were recorded in the Paris area (16 786 for neonates 34–36 WG and 329 376 for neonates ≥37 WG). The incidence of EOS was therefore 0.32 per 1000 live births: 1.49 per 1000 for late preterm infants (34–36 WG) and 0.26 per 1000 for term infants (≥37 WG) (table 1).

The 108 cases of EOS were 107 bacteraemia (including 14 associated with meningitis) and 1 meningitis with a negative blood culture. In term neonates, the most frequent pathogens were GBS (n=47) and *E. coli* (n=20), while in late preterm (34–36 WG) the most frequent were *E. coli* (n=15) and GBS (n=7) (table 2). The annual incidence of GBS EOS was 2.8 times higher in late preterm infants (0.42 per 1000 births) than in term infants (0.15 per 1000), and the incidence of *E. coli* EOS was 14 times higher in late preterm infants (0.89 per 1000) than in term infants (0.06 per 1000) (table 1).

Characteristics of mothers and infants

The characteristics of mothers and infants are described in table 3. The known antenatal risk factors among the population of infected neonates were intrapartum maternal temperature >38°C (38.0%), membrane rupture >12 hours (29.6%), unexplained preterm birth (18.5%), positive GBS screening test (15.1%) and history of neonatal GBS infection (2.8%) (table 3).

In addition, no GBS screening test was available at birth in 13.9%.

Clinical signs of infection were present in 97 infants (89.8%), most frequently (n=94) in the first 48 hours after birth. Eleven newborns remained asymptomatic, seven of them were born in chorioamnionitis background.

Antibiotic treatment within 3 days before labour onset had been administered to 16 (14.8%) women (amoxicillin alone or in combination): 14 in mothers of infants infected with *E. coli* (40%), while the 2 other infants were infected with *Klebsiella pneumoniae* and *Citrobacter koseri*, respectively. The reason was a prolonged membrane rupture for 15 of them and a pyelocaliceal dilatation for the last one. Out of 16 infants, 8 were born before 37 WG.

A total of 43 (39.8%) women received intrapartum antibiotic treatment, consisting mainly of amoxicillin alone or in combination (37 out of 43, 86.0%) (table 3).

E. coli infection was more frequent than GBS infection in the case of intrapartum antibiotic treatment (60.0% vs 22.2%) and membrane rupture >12 hours (60.0% vs 9.3%); moreover, no GBS infection was observed in the case of adequate intrapartum antibiotic treatment (table 3).

All infants had at least one C reactive protein measurement. C reactive protein was ≥10 mg/L for the first sample in 47.2% (n=51) and in 96.3% (n=104) for the maximal value in serial samples.

Antibiotic treatment of neonates and outcomes

The most frequent initial treatment of neonates was an amoxicillin–gentamicin combination (60.2%) (table 4). The initial treatment was modified in 55 infants (50.9%): in 19 cases (17.6%) the antibiotic spectrum was reduced and broadened in 36 cases (33.3%).

Almost all infants (93.5%) were transferred to another department (table 4). Of the 108 infants with EOS, 106 (98.1%) were discharged alive and 2 (1.9%) died during hospitalisation.

Antibiotic resistance

All GBS strains were susceptible to amoxicillin and only one had a high level of resistance to gentamicin (1.8%); 33.3% were resistant to clindamycin. Resistance to kanamycin/amikacin was assessed in 36 of the 54 GBS strains and 16.7% (6 out of 36) were found resistant.

Among the 35 *E. coli* isolates, 68.6% (24 out of 35) were resistant to amoxicillin and 14.3% (5 out of 35) produced an extended spectrum beta-lactamase and were resistant to cefotaxime (table 5). Five isolates (14.3%) were resistant to both amoxicillin and gentamicin, and four (11.4%) to both cefotaxime and gentamicin. Only one strain was resistant to amikacin. Of the 35 *E. coli* strains, 22 (62.9%) were K1, including all *E. coli* meningitis.

Among the 35 neonates infected with *E. coli*, 14 mothers did not receive any peripartum antibiotic therapy; 5 (35.7%) of these 14 *E. coli* strains were resistant to amoxicillin and only 1 out of 14 (7.1%) to cefotaxime (table 5). All were sensitive to gentamicin. One of the 35 mothers had an inadequate peripartum antibiotic therapy; the *E. coli* strain was sensitive to amoxicillin and gentamicin. Twenty mothers had an adequate peripartum antibiotic therapy, including 14 of them within 3 days before delivery. A total of 19 (95%) of these 20 *E. coli* strains were resistant to amoxicillin, 4 (20%) to cefotaxime, 5 (25%) to gentamicin and 1 (5%) to amikacin.

Table 5 Antibiotic resistance of 35 *Escherichia coli* strains

Case	Term (WG)	Diagnosis	ATB within 3 days	Intrapartum ATB prophylaxis	Antibiotic resistance					Initial EOS treatment*
					Amox	Cefo	Cipro	Genta	Amik	
1	34 ⁺⁶	Sepsis	No	No	R	S	S	S	S	cg
2	35 ⁺²	Sepsis/meningitis	No	No	R	R	S	S	S	ESBL cg
3	36 ⁺⁶	Sepsis	No	No	S	S	S	S	S	cg
4	37 ⁺¹	Sepsis	No	No	S	S	S	S	S	cvg
5	37 ⁺⁵	Sepsis	No	No	S	S	S	S	S	acg
6	37 ⁺⁶	Sepsis	No	No	R	S	S	S	S	ag
7	38 ⁺⁰	Sepsis	No	No	R	S	S	S	S	ag
8	38 ⁺¹	Sepsis	No	No	S	S	S	S	S	ag
9	38 ⁺⁴	Sepsis	No	No	S	S	S	S	S	ag
10	39 ⁺⁰	Sepsis	No	No	S	S	S	S	S	ag
11	39 ⁺⁴	Sepsis	No	No	R	S	S	S	S	acg
12	40 ⁺²	Sepsis	No	No	S	S	S	S	S	cg
13	41 ⁺⁰	Sepsis	No	No	S	S	S	S	S	ag
14	41 ⁺¹	Sepsis	No	No	S	S	R	S	S	acg
15	41 ⁺²	Sepsis/meningitis	No	Yes, inadequate	S	S	R	S	S	acg
16	34 ⁺³	Sepsis	Yes	Yes, adequate	R	R	R	R	R	ESBL ag
17	34 ⁺³	Sepsis	No	Yes, adequate	R	S	S	S	S	cg
18	34 ⁺⁴	Sepsis	Yes	Yes, adequate	R	S	S	S	S	cg
19	35 ⁺²	Sepsis	Yes	Yes, adequate	R	S	S	S	S	ag
20	35 ⁺³	Sepsis/meningitis	Yes	Yes, adequate	R	S	R	S	S	aA
21	35 ⁺⁴	Sepsis/meningitis	No	Yes, adequate	R	S	S	S	S	ag
22	35 ⁺⁵	Sepsis	No	Yes, adequate	S	S	S	S	S	ag
23	36 ⁺⁰	Sepsis/meningitis	Yes	Yes, adequate	R	S	S	S	S	ag
24	36 ⁺⁰	Sepsis	No	Yes, adequate	R	R	R	R	S	ESBL ag
25	36 ⁺⁰	Sepsis	Yes	Yes, adequate	R	S	R	S	S	ag
26	36 ⁺³	Sepsis	Yes	Yes, adequate	R	S	S	S	S	acg
27	36 ⁺³	Sepsis/meningitis	Yes	Yes, adequate	R	R	R	R	S	ESBL cA
28	37 ⁺⁴	Sepsis/meningitis	Yes	Yes, adequate	R	R	R	R	S	ESBL cg
29	39 ⁺¹	Sepsis	Yes	Yes, adequate	R	S	S	S	S	cg
30	39 ⁺⁴	Sepsis	Yes	Yes, adequate	R	S	S	S	S	cg
31	40 ⁺⁴	Sepsis/meningitis	Yes	Yes, adequate	R	S	S	S	S	acA
32	40 ⁺⁴	Sepsis	Yes	Yes, adequate	R	S	S	R	S	acg
33	40 ⁺⁵	Sepsis	No	Yes, adequate	R	S	S	S	S	ag
34	41 ⁺¹	Sepsis	Yes	Yes, adequate	R	S	S	S	S	cg
35	41 ⁺⁴	Sepsis	No	Yes, adequate	R	S	S	S	S	ag

*Initial EOS treatment: a, amoxicillin; A, amikacin; c, cefotaxime; g, gentamicin; v, vancomycin.

Amik, amikacin; Amox, amoxicillin; ATB, antibiotics; Cefo, cefotaxime; Cipro, ciprofloxacin; EOS, early-onset neonatal sepsis; ESBL, extended spectrum beta-lactamase; Genta, gentamicin; R, resistant; S, susceptible; WG, weeks of gestation.

DISCUSSION

We present for the first time the incidence, microbiology, epidemiology, mortality and risk factors for EOS in neonates ≥ 34 WG based on a 2-year prospective study performed among 346 162 newborns in all maternity wards in the largest region of France. We report an incidence of EOS in neonates ≥ 34 WG equal to 0.32 per 1000 live births (95% CI 0.26 to 0.38). The incidence was six times higher in the late preterm infants compared with those born at term (1.49 vs 0.26 per 1000, respectively).

In a retrospective study between 1993 and 2003 in 14 hospitals in the USA, Puopolo *et al*⁷ reported an incidence of EOS of 0.58 per 1000 live births ≥ 34 WG (1.2 per 1000 in the 34–36 WG group and 0.53 per 1000 in the ≥ 37 WG group). More recently, Stoll *et al*,⁴ in a prospective study in 18 Neonatal Research Network centres in the USA, observed an incidence of 0.73 per 1000 live births in late preterm neonates (34–36 WG) and 0.56 per 1000 live births in neonates at term.

GBS antepartum screening test was positive in 14 out of 93 (15.1%) mothers (15 women were not tested). This prevalence is consistent with that of a meta-analysis reporting an estimated mean prevalence of rectovaginal GBS colonisation of 19.0% (95% CI 16.1 to 22.0) in Europe.¹⁴ Universal culture-based screening for GBS carriage (vaginal swab) at 34–38 WG is recommended for pregnant women by the French National College of Obstetricians and Gynecologists.¹⁵ This examination is covered at 100% by social security. Since the generalisation of GBS screening and peripartum antibiotic prophylaxis, the majority of cases of GBS-associated EOS have occurred in newborns whose mothers have been screened negative for GBS.^{7 16} In our study, this rate was 76% (35 out of 46). Six other mothers (4 GBS and 2 *E. coli*) had not been screened for GBS and had no other EOS risk factors. We can speculate that more GBS EOS would have been prevented by peripartum sensitive GBS screening test using PCR. Indeed, 71 maternity

wards used only prepartum culture for GBS screening, 8 used peripartum PCR in addition to prepartum culture and 2 only peripartum PCR. Of note, no GBS EOS occurred after adequate intrapartum antibiotic treatment.

The French guidelines for EOS in infants ≥ 34 WG are based on the assessment and stratification of infectious risk to initiate a reinforced clinical monitoring (online supplemental file 1).¹³ There was no antepartum or peripartum risk factor in 34 cases of EOS (31.5%) in our cohort. Thus, our results confirm that an infection cannot be ruled out in infants without perinatal risk factors. Furthermore, 29% (10 out of 34) of these infants with no risk factors became symptomatic within 12 hours after birth (5 GBS, 2 *E. coli*, 1 *Campylobacter jejuni*, 1 *K. pneumoniae* and 1 *Proteus mirabilis*).

Consistent with our results, several studies reported that 80%–90% of infants became symptomatic within the first 48 hours after birth.^{17–18} In our study, 10.2% of infants remained asymptomatic. Cantoni *et al*¹⁹ found no difference in clinical outcomes in term infants who were monitored with serial physical examinations versus those who additionally received laboratory testing. Escobar *et al*,²⁰ using a predictive EOS risk model, stated that the risk of EOS in asymptomatic infants was very low. Wortham *et al*,²¹ in a prospective study of EOS conducted among 396 586 living births in 16 US centres from 2006 to 2009, reported 389 cases of EOS. Records of 229 of them born to mothers with chorioamnionitis were reviewed and the authors found 21 (9%) infants who remained asymptomatic within 72 hours after birth. Altogether, these results suggest that clinical monitoring alone may not be sufficient to detect all EOS. Thus, the 11 cases of asymptomatic EOS were diagnosed after gastric aspirate or C reactive protein measurement. Compared with blood culture, laboratory tests currently used, such as C reactive protein²² or procalcitonin,²³ have however poor positive predictive value and lack specificity.

Empiric antibiotics were administered to most infants, generally amoxicillin–gentamicin combination (60.2%) according to the recent French recommendations for suspected EOS in infants ≥ 34 WG without signs of severity.¹³ Amoxicillin was ineffective in almost all *E. coli* strains (19 out of 20) from mothers who received amoxicillin within 3 days before delivery or as adequate peripartum antibiotic prophylaxis.

The strengths of this observational study are mainly its prospective design, the inclusion of all maternity wards of a region and the recapture of all EOS cases via the microbiology laboratories associated with these maternity wards. All parents of infants with EOS gave their consent and all infants with EOS were born in the Paris area (no transfer from another region). The recovery of all EOS cases was therefore systematic and we can assume quasi-exhaustiveness. Our study provides, for the first time, a reliable EOS rate in the largest region of France for the overall neonatal population and according to pathogens and pregnancy term. The limitations of the study are mainly related to the fact that we did not know the exact duration of membrane rupture (only ≤ 12 hours or > 12 hours was recorded) and the exact value of maternal peripartum temperature ($\leq 38^\circ\text{C}$ or $> 38^\circ\text{C}$). In addition, we did not differentiate chorioamnionitis from isolated maternal fever peripartum.

In conclusion, the EOS rate was 0.32 per 1000 live births in neonates aged ≥ 34 WG born in the Paris area. EOS was six times more frequent in late preterm infants; GBS was twice as frequent as *E. coli* in term infants, but this ratio was reversed in late preterm infants. These data encourage the use of the PCR method for screening of GBS during labour. Monitoring

EOS epidemiology, and in particular the incidence of Gram-negative bacteria and their rate of antibiotic resistance, seems fundamental to adjust EOS empiric treatment.

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Contributors PS initiated the study, wrote the protocol, implemented the study in all neonatology departments, maternity wards and bacteriological laboratories, was responsible for study data and analysis, wrote the article and was the guarantor of the study. SB was responsible for the study of *E. coli* strains and participated actively in the study and in writing the article. CP was responsible for the study of group B *Streptococcus* strains. VB, LF-L and PB participated in the writing of the successive versions of the manuscript. All authors validated the final version of the manuscript.

All members of the EOS study group were responsible for the reporting of cases of EOS occurring in their departments and completed forms.

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SUPPLEMENTAL DATA

French recommendations for newborns at risk of EOS (French Society of Neonatology, French Society of Pediatrics. Management of the newborn at risk of early neonatal bacterial infection (≥ 34 WG). September 2017.

https://www.sfpediatric.com/sites/www.sfpediatric.com/files/documents/label_has_recommandations_inbp.09.2017.pdf.

Grade of recommendations:

Grade A: Scientific evidence established

Grade B: Scientific presumption

Grade C: Low level of evidence

Grade AE: Agreement of experts

1. Identification of newborns at risk for EOS

Demonstrated antenatal risk factors for EOS include the following (Grade A):

- Maternal GBS colonization during the current pregnancy (positive GBS vaginal swab either by culture or rapid PCR in the intrapartum period, and/or GBS bacteriuria)
- A history of neonatal GBS infection in a previous pregnancy
- A duration of rupture of the membranes greater than 12 hours
- Spontaneous and unexplained prematurity < 37 WG
- Maternal fever $>38.0^{\circ}\text{C}$ peripartum (or within 2 hours of delivery).

Among these situations, those for which antibiotic prophylaxis or antibiotic therapy peripartum is indicated are the followings:

- Maternal fever $>38.0^{\circ}\text{C}$ isolated or not (associated signs of chorioamnionitis) during peripartum, regardless of vaginal swab status (Grade A)
- Maternal GBS colonization during the current pregnancy* (GBS-positive vaginal swab either by culture or rapid PCR peripartum, and/or GBS bacteriuria) (Grade A)

- A history of neonatal GBS infection in a previous pregnancy (Grade A)
- In case of unknown vaginal swab status (culture not performed or result not available, intrapartum rapid PCR with invalid or unavailable result) (Grade B) and:
 - o duration of rupture of membranes > 12 hours
 - or
 - o spontaneous and unexplained prematurity < 37 WG

* with the exception of those who delivered by cesarean section before the onset of labor and with intact membranes.

The criteria for adequate antibiotic prophylaxis or intrapartum antibiotic therapy are as follows (Grade B):

Maternal antibiotic therapy should be administered

- Intravenously
- At least 4 hours before birth
- Using penicillin G, ampicillin or amoxicillin, or cefazolin

Any other antibiotic treatment (molecule, modality and time of administration less than 4 hours before birth) will be considered inadequate.

In total, a newborn should be considered at risk of EOS when antibiotic prophylaxis or intrapartum antibiotic therapy was indicated (Grade A).

The pediatrician, obstetrician, and midwife should ascertain the indications for and adequacy of antibiotic prophylaxis or therapy to assess the newborn's level of risk for EOS (Grade AE).

The adequacy or inappropriateness of antibiotic prophylaxis or antibiotic therapy peripartum should define the level of surveillance of neonates at risk for EOS (Grade C).

2. Asymptomatic newborns with risk factors for EOS:

Asymptomatic newborns at risk for EOS are defined by the presence of one or more EOS risk factors. They should be monitored specifically in maternity ward or in the appropriate level of care (Grade C).

Asymptomatic newborns at risk for EOS can be classified into one of three categories:

Category A: Newborns whose mother has received adequate peripartum antibiotic prophylaxis for:

- maternal GBS colonization
- or a history of neonatal GBS infection
- or rupture of membranes longer than 12 hours
- or spontaneous, unexplained prematurity

Category B: Newborns whose mother has received inadequate peripartum antibiotic prophylaxis (including no antibiotic prophylaxis when indicated), or whose mother has received adequate peripartum antibiotic therapy for fever $> 38^{\circ}\text{C}$.

Category C: Neonates whose mother has received, for a fever $> 38^{\circ}\text{C}$, inadequate peripartum antibiotic prophylaxis or antibiotic therapy.

Recommendations for surveillance of asymptomatic newborns at risk of EOS ≥ 36 WG:

- Newborns in **Category A:**

- Routine postpartum surveillance (Grade C).
- No discharge before 48 hours (Grade C).

- Newborns in **Category B:**

- Standardized monitoring after delivery every 4 hours for the first 48 hours using a monitoring grid, which should be adapted to local maternity conditions (Grade C).
- The appearance of any clinical sign requires immediate clinical examination by the pediatrician and the performance of additional tests as well as the initiation of antibiotic therapy, if necessary, after taking a blood sample for culture (Grade B).

- Newborns in **Category C.** Those at highest risk for EOS:

- Standardized monitoring after delivery every 4 hours during the first 48 hours, which should be adapted to local maternity conditions (Grade C).
- Clinical examination by a pediatrician between H6 and H12 (Grade AE).
- The occurrence of a clinical sign in this setting requires the administration of empiric antibiotics as soon as possible after taking a blood sample for culture (Grade B).

Recommendations for surveillance of asymptomatic neonates in categories A, B, and C < 36 WG (and \geq 34 WG).

- Admission to the appropriate level of care (“kangaroo unit”, Neonatology)
- Monitoring adapted to their prematurity and the level of risk of EOS (Grade C).

Specific surveillance procedures for asymptomatic newborns at risk for EOS

The clinical criteria used for the standardized monitoring grid are temperature, heart rate, respiratory rate, signs of respiratory distress, and skin discoloration (Grade C).

It is recommended to call the midwife or pediatrician if the following clinical signs occur (Grade AE):

- Temperature \geq 38.0°C or $<$ 36.0°C,
- Heart rate $>$ 160/min or $<$ 80/min,
- Respiratory rate $>$ 60/min,
- Presence of grunting or apnea,
- Abnormal skin color: pallor, cyanosis, mottling, or gray color
- Any clinical sign or change in condition that concerns the health care team.

3. Additional tests for newborns at risk for EOS

3.1. Blood culture

Blood culture is the recommended reference test for the etiological diagnosis of EOS (Grade A).

It is recommended that a blood culture be obtained for any newborn presenting with clinical signs of EOS prior to initiation of empiric antibiotic therapy (Grade B).

Blood cultures for surveillance of asymptomatic neonates at risk for EOS is not recommended (Grade B).

3.2 Lumbar puncture

It is recommended that lumbar puncture be performed in the management of the risk of EOS in newborns ≥ 34 weeks of age under the following conditions :

- Blood culture positive for a pathogenic germ (Grade A)
- Newborns with impaired general condition or neurological signs provided that their clinical condition is compatible with the performance of the procedure (Grade B).

3.3. Gastric fluid and superficial (peripheral) sampling

Gastric fluid sampling and peripheral samplings (ears and anus) are no longer recommended for the management of the EOS risk in newborns ≥ 34 weeks WG (Grade B).

3.4 Complementary non-bacteriological tests to be performed at birth

It is no longer recommended that a blood count or C-reactive protein be performed at birth as part of the diagnostic process for EOS (Grade B).

It is not recommended to perform C-reactive protein or procalcitonin be performed at birth when initiating antibiotic therapy in a newborn with suspected EOS (Grade B).

It is recommended that a CRP test be performed at initiation of antibiotic therapy in a neonate with suspected EOS when therapy is initiated after 12 hours of live (Grade C).

The use of a CRP 24 and 48 hours after the start of antibiotic therapy may be useful in supporting the decision to discontinue antibiotic therapy in a newborn with a negative blood culture at 48 hours (Grade C).

The cord blood procalcitonin result in a newborn at risk for EOS is not relevant to the indication for postnatal antibiotic therapy (Grade AE).

Procalcitonin testing in a newborn with suspected asymptomatic or symptomatic EOS is not recommended (Grade B).

4. Antibiotic therapy for EOS

Recommendations for empiric antibiotic therapy

Recommended treatment strategy (Grade AE):

- First-line in newborns ≥ 34 WG suspected of EOS and symptomatic without signs of severity

- o amoxicillin 100 mg/kg/24h in 2 IV 20 minute injections direct IV
- o gentamicin in 1 IV 30-minute injection:
 - 5 mg/kg/24h in neonates \geq 37 WG
 - 6 mg/kg/24h in newborn 34-36 WG
- If there are signs of severity (hemodynamic disorders or neurological clinical signs) possibly caused by infection:
 - o cefotaxime 200 mg/kg/24h in 2 IV 20-minute injections or direct IV
 - o gentamicin in 1 IV 30-minute injection
 - 5 mg/kg/24h in neonates \geq 37 WG
 - 6 mg/kg/24h in newborn 34-36 WG
 - o If listeriosis is suspected, add amoxicillin at a dosage of 100 mg/kg/24h in two 20-minute IV injections or direct IV.
- In the case of documented ongoing maternal infection (urinalysis, blood culture) with a pathogen other than GBS, it is recommended that the isolated bacterium be taken into account and its antibiogram in order to adapt the first-line antibiotic therapy in the newborn:
 - o If maternal urinalysis or blood culture is positive for *Escherichia coli*: biotherapy with cefotaxime (100 mg/kg/24h in two 20-minute IV injections or direct IV + gentamicin 30-minute IV injection;
 - o If maternal urinalysis or blood culture is positive for *Escherichia coli* ESBL, seek expert advice to decide on the most appropriate antibiotic therapy.
- The use of ceftriaxone in neonates as part of the management of EOS is contraindicated.

Recommendations for adapting initial empiric antibiotic therapy

- Discontinuation of antibiotic therapy should be considered as early as 48 hours after the start of treatment. The continuation of antibiotic treatment is not justified if the blood culture is sterile, if the clinical examination is normal, and if there is stability or a decrease of the C-reactive protein (Grade AE).
- Discontinuation of antibiotic therapy 48 hours after the start of treatment must be accompanied by clinical monitoring for an additional 24 to 48 hours at the clinician's discretion (Grade AE).

- Continuation of antibiotic therapy for forms with initial signs of severity (hemodynamic disorders or clinical neurological signs) possibly caused by the infection in the absence of bacteriological documentation should be done after assessment by the pediatrician (Grade AE).
- In a newborn whose clinical condition, without initial signs of severity, is strongly suggestive of infection in the absence of bacteriological documentation at 48 hours after the onset of the infection, the continuation of antibiotic therapy should be based according to the pediatrician's assessment (Grade AE).
- Antibiotic therapy should be continued if an infection is documented by blood culture or cerebrospinal fluid, adapting it to the bacterium identified (Grade AE).
 - o In the case of confirmed infection with positive blood culture and in the absence of meningeal location: discontinuation of gentamicin after two doses and treatment continuation with beta-lactam therapy:
 - If blood culture positive for *Streptococcus agalactiae*: amoxicillin 100 mg/kg/24h in two 20-minute IV injections or direct IV for 7 days.
 - If blood culture positive for *Escherichia coli* (even if ampicillin S): cefotaxime 100 mg/kg/24h in two 20-minute IV injections or direct IV for 7 days
 - If blood culture is positive for another germ: seek specialized advice
 - o In case of meningitis, gentamicin should be given for 2 to 5 days and beta-lactam therapy should be continued:
 - In case of *Streptococcus agalactiae* meningitis: amoxicillin 200 mg/kg/24h in two 20-minute IV injections or direct IV for a total treatment duration of 14 days.
 - In case of *Escherichia coli* meningitis: cefotaxime 200 mg/kg/24h in two 20-minute IV injections or direct IV until 7 days after birth then cefotaxime 200 mg/kg/24h in four 20-minute IV injections or direct IV for a total duration of 21 days.
 - In case of meningitis with another germ: seek specialized advice.

Figure S1. French recommendations for clinical monitoring of asymptomatic newborns at risk of EOS (French Society of Neonatology, French Society of Pediatrics. Management of the newborn at risk of early neonatal bacterial infection (≥ 34 WG). September 2017.

https://www.sfpediatric.com/sites/www.sfpediatric.com/files/documents/label_has_recommandations_inbp.09.2017.pdf.

