**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.sfpediatrie.com/sites/www.sfpediatrie.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°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°C isolated or not (associated signs of chorioamniotitis) 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)



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- 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:



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**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°C.

**Category C**: Neonates whose mother has received, for a fever > 38°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).



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**Recommendations for surveillance of asymptomatic neonates in categories A, B, and C < 36 WG (and ≥ 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 ≥ 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).



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### 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 ≥ 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 ≥ 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.sfpediatrie.com/sites/www.sfpediatrie.com/files/documents/label_has_recommandations_inbp.09.2017.pdf).