

SPECIAL ARTICLE

Management of the newborn at risk for vertical sepsis



Belén Fernández Colomer^{a,*}, Concepción de Alba Romero^b, Ana Alarcón Allén^c,
Fátima Camba Longueira^d, María Cernada^e, Zenaida Galve Pradel^f,
María González López^g, María Cruz López Herrera^h, Laura Sánchez Garcíaⁱ,
Elena Zamora Flores^j, en representación de la Comisión de Infección Neonatal de la
Sociedad Española de Neonatología

^a Servicio de Neonatología, Hospital Universitario Central de Asturias, Oviedo, Spain

^b Servicio de Neonatología, Hospital Universitario 12 de Octubre, Madrid, Spain

^c Servicio de Neonatología, Hospital San Joan de Deu y Hospital Clínic, Barcelona, Spain

^d Servicio de Neonatología, Hospital Universitario Vall d'Hebron, Barcelona, Spain

^e Servicio de Neonatología, Hospital Universitari i Politècnic La Fe, Valencia. Grupo de investigación en Perinatología, Instituto de Investigación Sanitaria La Fe (IIS La Fe), Valencia, Spain

^f Servicio de Neonatología, Hospital Universitario Miguel Servet, Zaragoza, Spain

^g Servicio de Neonatología, Hospital Materno-Infantil Regional Málaga, Málaga, Spain

^h Servicio de Neonatología, Hospital Universitario Cruces, Barakaldo, Spain

ⁱ Servicio de Neonatología, Hospital Universitario La Paz, Madrid, Spain

^j Servicio de Neonatología, Hospital Universitario Gregorio Marañón, Madrid, Spain

Received 12 November 2025; accepted 26 November 2025

Available online 16 February 2026

KEYWORDS

Early-onset neonatal
sepsis;
Vertical transmission;
Newborn;
Premature;
antibiotics;
GBS;
Escherichia coli

Abstract Suspected early-onset sepsis (EOS) is one of the most frequent diagnoses in neonatal units; however, infection is not confirmed in most cases, leading to the widespread overuse of empirical antibiotherapy. This document presents a diagnostic and therapeutic approach to EOS and proposes evidence-based recommendations, supported by national epidemiological data, for the management of neonates at risk of EOS according to gestational age and individual risk level, in order to promote rational use of antibiotics in the neonatal period.

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DOI of original article: <https://doi.org/10.1016/j.anpedi.2025.504106>

* Corresponding author.

E-mail address: belen.fernandezc@sespa.es (B. Fernández Colomer).

PALABRAS CLAVE

Sepsis;
 Transmisión vertical;
 Neonato;
 Prematuro;
 Antibióticos;
 EGB;
Escherichia coli

Manejo del recién nacido con riesgo de sepsis vertical

Resumen La sospecha de sepsis vertical es uno de los diagnósticos más frecuentes en las unidades neonatales, si bien, en la mayoría de los casos la infección no se confirma, con la consiguiente sobreutilización de antibioterapia empírica y los posibles efectos adversos a corto y largo plazo. En este documento se presenta el abordaje diagnóstico y terapéutico de la sepsis vertical y se proponen recomendaciones basadas en la evidencia y en datos epidemiológicos nacionales, para optimizar el manejo del recién nacido con riesgo de sepsis vertical en función de su edad gestacional y nivel individual de riesgo, con el fin de promover el uso racional de la antibioterapia en el periodo neonatal.

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Introduction

Vertical sepsis (VS), also known as early-onset sepsis, continues to be a significant cause of morbidity and mortality in newborn infants today. It results from the colonization of the fetus or neonate by pathogens present in the maternal genital tract or, in rare cases, through transplacental hematogenous spread. The administration of intrapartum antibiotic prophylaxis under certain maternal circumstances and early administration of antibiotics upon suspicion of VS in the neonate have achieved a reduction in the incidence and severity of VS.¹ However, this approach is not without risks, which chiefly concern the short- and long-term consequences for the pregnant mother/fetus or the neonate of the exposure to antibiotics.² Therefore, identifying which neonates require early antibiotherapy and when or under what conditions to stop it is of utmost importance. The aim of this article is to provide updated information on the epidemiology of VS based on nationwide data from the Grupo Castrillo Neonatal Network³ and, based on this information, to update the recommendations for the management and treatment of neonates at risk of or with suspected VS.

Definition of vertical sepsis

Confirmed vertical sepsis is defined by isolation in blood culture of a pathogenic organism combined with the development of clinical manifestations of sepsis (Table 1) within 3 days of birth (≤ 72 h), which is why it is also known as early-onset neonatal sepsis. Although, based on data from the Grupo Castrillo Neonatal Network, up to 95% of cases have onset in the first 3 days post birth, the window for the onset of symptoms can extend to 7 days post birth. However, confirmation of vertical transmission in such cases requires identification of perinatal risk factors for infection (maternal colonization by *Streptococcus agalactiae*/Group B *Streptococcus* [GBS], prolonged rupture of membranes, chorioamnionitis or spontaneous preterm labor), ruling out nosocomial infection, and isolation in culture of a pathogen commonly involved in vertical sepsis (GBS, *Escherichia coli*).

Suspected vertical sepsis is one of the most common diagnoses in neonatology, and the condition is suspected based

Table 1 Signs and symptoms of neonatal sepsis.

Respiratory signs	Hemodynamic signs
Respiratory distress: grunting, nostril flaring, chest retractions, etc.	Bradycardia: heart rate < 100 bpm, at least 3 episodes lasting 20 s in a three-hour period and requiring active intervention.
Persistent tachypnea that does not respond to routine supportive care	Tachycardia.
Apnea: longer than 20 s, recurrent, and requiring active intervention.	Hypotension.
Neurologic signs	Gastrointestinal signs
Irritability: unexplained by pain.	Food refusal.
Hypotonia.	Poor enteral tolerance.
Lethargy	Abdominal distension.
Seizures: clinical or electrical	Bloody stools.
Cutaneous signs	Other
Jaundice.	Hypothermia (more frequent in preterm infants)
Yellowish, pale-greyish hue.	Hyperthermia
Slow capillary refill	Hypo/Hyperglycemia
Purpura, petechiae.	Metabolic acidosis

on the presence of clinical signs suggestive of infection and/or elevation of biomarkers associated with infection (C-reactive protein [CRP], procalcitonin [PCT], interleukin-6 [IL-6]) in a newborn infant, especially when there are perinatal risk factors for infection. This clinical picture prompts hospital admission of the neonate and initiation of empirical antibiotherapy, which in many cases is maintained for a prolonged period despite negative blood culture results, the low positive predictive value of current biomarkers, and the low incidence of vertical sepsis.⁴ In this context, the term

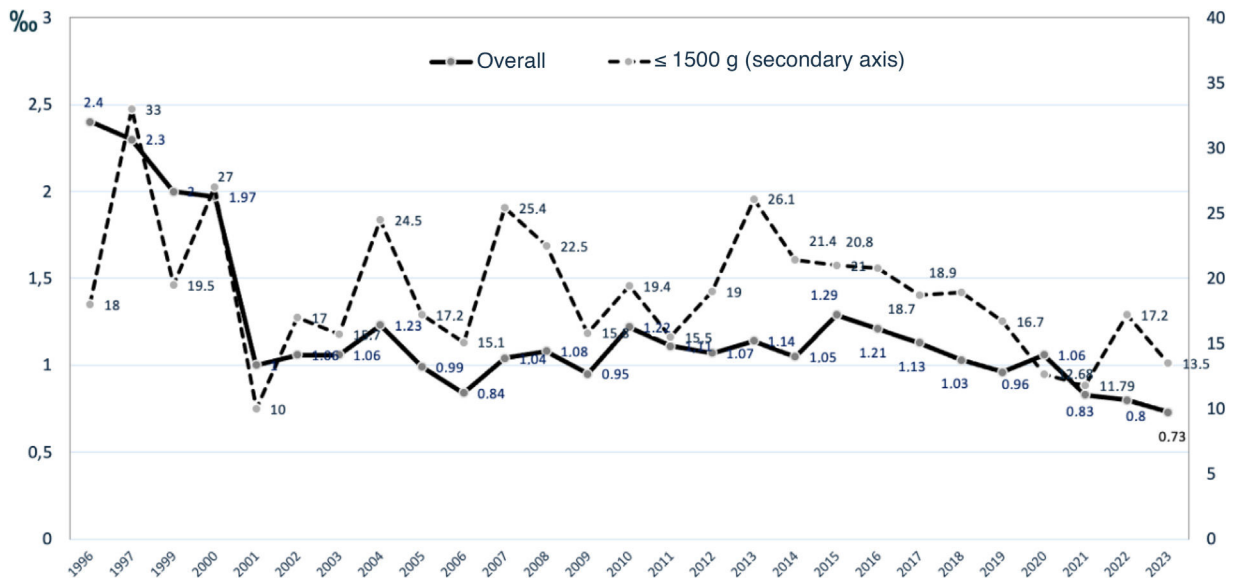


Figure 1 Temporal trends in the incidence of confirmed vertical sepsis per 1000 live births, overall (solid line) and in infants with birth weight ≤ 1500 g (dotted line), in the 1996–2023 period in Spain. Source: Grupo Castrillo Neonatal Network.

“clinical vertical sepsis” is used to refer to infants born to mothers with perinatal risk factors for infection and who received intrapartum antibiotherapy, who present with suggestive symptoms and elevation of biomarkers in the first 3 days post birth, and who receive a complete course of antibiotherapy despite negative blood culture results.⁵

Epidemiology of vertical sepsis

The incidence of VS in Spain has declined significantly since the implementation in 1998 of the strategy for the prevention of perinatal infection by GBS (the most common cause of vertical sepsis at that time), and is currently among the lowest in the world.³ This international strategy, adopted and endorsed by several scientific societies in Spain (Spanish Society of Neonatology [SENeo] and Spanish Society of Gynecology and Obstetrics [SEGO], among others) continues to be the only available effective preventive measure. It is based on the universal screening of GBS in pregnant women with administration of intrapartum antibiotherapy to carriers and establishing the indication of prophylaxis in mothers of unknown carriage status based on the presence of risk factors.^{6,7}

The generalized implementation of this preventive protocol has changed epidemiological trends in vertical sepsis worldwide.⁸ In Spain (Fig. 1), its incidence has decreased by 60% (from 2.4 cases per 1000 live births in 1996 to 1–1.2 cases per 1000 live birth since 2001) and a significant shift in its etiology, with GBS accounting for 50% of cases of sepsis in 1996 compared to less than 30% at present (from 1.2 cases per 1000 live births to 0.2–0.3 per 1000), as cases caused by *Escherichia coli* surged, going from 12% to 30% of cases, and becoming the leading cause of vertical sepsis in preterm neonates (5–11 cases per 1000 live births with birth weight ≤ 1500 g) (Fig. 2A and B). Other pathogens involved in vertical sepsis include *Enterococcus* spp (and other streptococci) and *Listeria monocytogenes* among the gram-positive bac-

Table 2 Pathogens isolated in 3138 episodes of confirmed vertical sepsis in the 1996–2023 period in Spain. Source: Grupo Castrillo Neonatal Network.

Pathogen	Cases	Percentage
Gram-positive	1887	60.13
<i>Streptococcus agalactiae</i> (GBS)	1058	33.72
<i>Enterococcus</i> spp	247	7.87
<i>Streptococcus</i> spp (other)	196	6.24
<i>Listeria monocytogenes</i>	187	5.96
<i>Staphylococcus aureus</i>	73	2.33
Coagulase-negative <i>Staphylococcus</i> spp	100	3.18
Other	26	0.83
Gram-negative	1212	38.62
<i>Escherichia coli</i>	920	29.32
<i>Klebsiella</i> spp	102	3.25
<i>Haemophilus</i> spp	47	1.50
<i>Enterobacter</i> spp	36	1.15
<i>Morganella morganii</i>	19	0.61
<i>Pseudomonas</i> spp	20	0.64
Other	68	2.17
Candida spp	39	1.24
Total	3138	

Source: Grupo Castrillo Neonatal Network.

teria and *Klebsiella* spp among the gram-negative bacteria³ (Table 2).

The reported mortality of confirmed VS ranges between 8% and 10% overall, increasing to 30% in infants with birth weight of less than 1500 g. Besides gestational age, other factors associated with mortality are the presence of intrauterine infection, the isolated pathogen (*E coli*) or the presence of multidrug-resistant bacteria.³

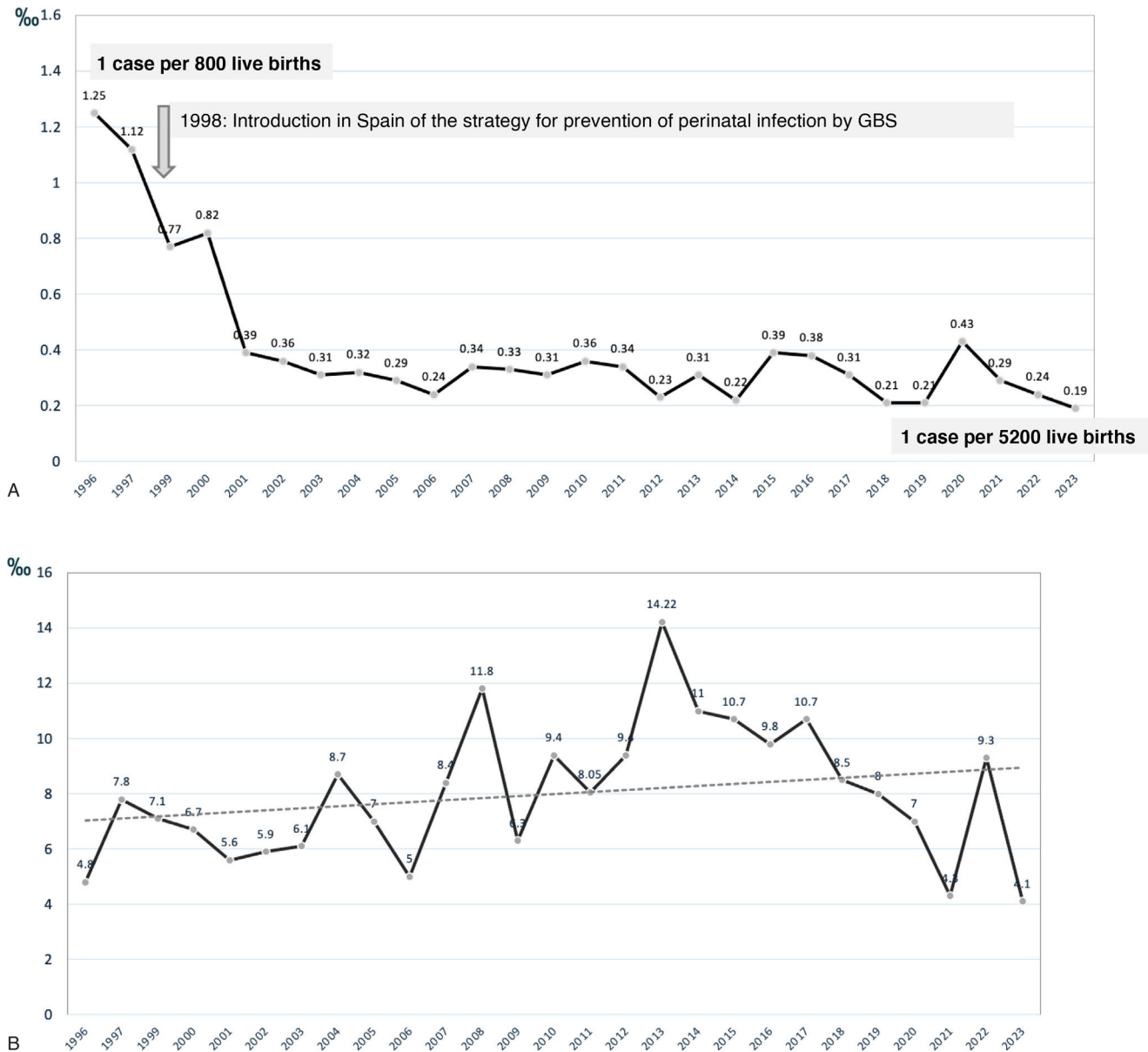


Figure 2 (A) Temporal trends in the incidence of confirmed vertical sepsis caused by GBS per 1000 live births in the 1996–2023 period in Spain. Source: Grupo Castrillo Neonatal Network. (B) Temporal trends in the incidence of confirmed vertical sepsis caused by *E. coli* in infants with birth weight ≤ 1500 g per 1000 live births in the 1996–2023 period in Spain. Source: Grupo Castrillo Neonatal Network.

Risk factors

The main perinatal risk factors are:

- Maternal colonization by GBS in the absence of adequate intrapartum antibiotic prophylaxis (IAP).
- Spontaneous preterm labor (<37 weeks of gestation).
- Prolonged rupture of membranes ≥ 18 h.
- Suspected or confirmed intrauterine inflammation, infection or both ("Triple I") based on the presence of maternal fever $\geq 39^\circ\text{C}$ or fever between 38.0 and 38.9°C lasting more than 30 min accompanied by at least one of the following: fetal tachycardia (>160 bpm for ≥ 10 min), maternal leukocytosis with a white blood cell count

greater than $15.000/\text{mm}^3$ (without administration of corticosteroids) or purulent cervical discharge. Maternal tachycardia, uterine irritability or contractions and the elevation of inflammatory markers (such as CRP) are not considered diagnostic criteria for Triple I, although their presence support the diagnosis. Confirmation of Triple I requires evidence of bacterial growth in amniotic fluid or histopathologic evidence of infection in the placenta.⁹

Neonatal sepsis calculator. It is a tool based on a multivariate predictive model that combines perinatal maternal risk factors and variables related to the clinical presentation of the neonate to estimate the individual risk of VS in a particular infant and act according to the calculated risk.

Multiple studies attest to its usefulness, reporting a significant reduction in unnecessary antibiotherapy (40%–60%), performance of laboratory tests and neonatal admissions for suspected sepsis, with no associated increase in adverse events (mortality). Some of its limitations are the restriction of its use to the first 12–24 h of life (there are cases of VS with later onset), the need for staff qualified in the clinical assessment of the neonate (detection of signs of infection) and that it cannot be applied to infants born before 34 weeks of gestational age. It is available as a web calculator and as a mobile app.^{10,11}

Although the risk of VS is inversely proportional to gestational age (GA), it is possible to identify preterm infants at low risk of sepsis (cesarean delivery for maternal indications, absence of labor or rupture of membranes and absence of suspicion of intra-amniotic infection) in whom empirical antibiotherapy may be withheld if they show no clinical signs of VS.¹²

Prevention of vertical sepsis caused by GBS

The current prevention strategy is based on the identification of pregnant women colonized by GBS (10%–30% of pregnant women) and administration of IAP to carriers or, in the subset of women of unknown carriage status, those with risk factors (Table 3).^{6,7} Its implementation, as noted above, has been followed by sharp decline in VS from GBS, and, in fact, most of the cases recently reported tend to be related to false negatives from vaginal-rectal cultures resulting in failure to deliver IAP.

During pregnancy, screening for GBS through a vaginal-rectal culture is indicated in the following cases:

- All pregnant women between 36⁺⁰ and 37⁺⁶ weeks of gestation.
- Previous culture performed more than 5 weeks before delivery that was negative for GBS.
- Labor before 37⁺⁰ weeks, with or without rupture of membranes.
- In the case of preterm or term prelabor premature rupture of membranes.

Vaginal-rectal culture is not necessary in pregnant women who have had a previous child with neonatal GBS infection or if GBS has been detected in urine during the current pregnancy (both cases in which administration of IAP is indicated).

Intrapartum antibiotic prophylaxis is considered complete if at least one dose of penicillin, ampicillin, or cefazolin has been administered at least 4 h before delivery. Any other antibiotic or time window should be considered inadequate or insufficient.

Intrapartum antibiotic prophylaxis is not effective for prevention of late-onset sepsis from GBS.

Diagnostic methods

Signs of infection in neonates are nonspecific and tend to be few. Neonates with bacterial sepsis may exhibit systemic or focal signs and symptoms of infection, including respiratory distress, thermal instability, hypotension, poor perfusion,

Table 3 Indications for intrapartum antibiotic prophylaxis (IAP).

IAP indicated	IAP not indicated
Positive vaginal-rectal culture performed at the end of current pregnancy*	Negative vaginal-rectal culture in current pregnancy (performed in the 5 weeks prior to delivery), regardless of risk factors, even if it was positive in a previous pregnancy.
Positive intrapartum molecular test for detection of GBS carriage**	Cesarean delivery before onset of labor and without rupture of membranes, regardless of gestational age and GBS carriage status.
Detection of GBS in urine in any trimester of current pregnancy.	Pregnancies of more than 37 weeks with unknown maternal carriage status and no known risk factors.
Previous child with invasive GBS infection.	
Unknown carriage status at the time of delivery (or negative result in culture performed > 5 weeks before delivery) and any of the following	
Delivery before 37 weeks ^a	
Rupture of membranes ≥ 18 h.	
Maternal intrapartum fever ≥ 38.0 °C. ^b	
GBS-positive in previous pregnancy.	

* The optimal timing for vaginal-rectal culture is between weeks 36⁺⁰ and 37⁺⁶.

** If molecular test (PCR) is negative, but there are risk factors, IAP is also indicated.

^a In the case of anticipated preterm birth, a vaginal-rectal culture for GBS should be performed and prophylaxis for perinatal GBS infection initiated, independently of any other indicated interventions, such as those for premature rupture of membranes or Triple I, which are not discussed in this document.

^b In the case of suspected Triple I, broaden the spectrum of antibiotic coverage.

pallor, abnormal heart rhythms, apnea, irritability, lethargy, and seizures, among others (Table 1).

None of the biomarkers that are currently available can be used to diagnose neonatal sepsis with sufficient sensitivity and specificity. The most commonly used diagnostic methods are:

Blood culture. It is the gold standard for diagnosis of VS. Advances in blood culture processing, such as automation and the use of mass spectrometry techniques, have reduced the time required to detect bacterial growth, facilitating the early discontinuation of empirical antibiotherapy. Blood culture media contain antibiotic-binding resins that limit the antimicrobial activity of any antibiotics present in the blood sample, allowing bacteremia to be identified at a level of

1–10 colony-forming units (CFU) per mL. Blood culture volumes of at least 1 mL maximize the probability of growth in cases where the bacterial load in the bloodstream is low. Smaller volumes may reduce the sensitivity and increase the risk of contamination and the time required for any microorganism to grow.^{13,14}

Molecular techniques based on the identification of bacterial DNA/RNA in biological samples. These novel techniques are increasingly used to identify the presence of microorganisms in blood and other biological fluids. Their advantages include faster identification (less than 12 h), requiring smaller blood volumes (they can even be performed on the same sample used for blood culture), greater sensitivity and specificity, and the ability to simultaneously detect multiple pathogens and even antibiotic resistance genes (nested multiplex polymerase chain reaction). The disadvantages are that they cannot differentiate between infection and contamination (so the clinical evaluation continues to be a priority), the cost is still high, and they are not available in every hospital.^{15,16}

Cerebrospinal fluid (CSF) analysis. Identifying meningeal involvement is essential, as it affects decisions regarding the dose, type and duration of antibiotic treatment, and it is associated with a higher morbidity, mortality, and incidence of long-term sequelae. In the experience of the Grupo Castrillo network, the incidence of vertical meningitis is 0.2 cases per 1000 live births (10%–20% of vertical sepsis cases are associated with meningitis). Given its incidence, lumbar puncture should be performed when there is a strong suspicion of sepsis and/or the clinical presentation is suggestive of meningitis. Preferably, it should be performed before initiation of antibiotherapy, although it can be delayed if the patient is unstable, without delaying antibiotherapy to await its performance.¹⁷

White blood cell differential. Abnormal findings in this test should not be used to make the diagnosis of sepsis, as the white blood cell count can be elevated in conditions involving inflammation without infection, such as chorioamnionitis, complicated delivery, pneumothorax, seizures, perinatal asphyxia, meconium aspiration syndrome, or maternal fever, and neutropenia in cases of preeclampsia, maternal use of corticosteroids, and even cesarean delivery.^{15,18} Counts higher than 20 000/mm³ or below 5000/mm³ have been associated with the presence of VS, but offer a very low sensitivity. The white blood cell count changes in the first days of life, so serial counts could be useful. As for the immature/total neutrophil ratio (I/T), the value range associated with the presence of neonatal sepsis is ≥ 0.2 up to 72 h post birth and ≥ 0.12 thereafter.

Acute phase reactants

- **C-reactive protein (CRP):** like white blood cell counts, CRP levels increase under inflammatory conditions (maternal fever, fetal distress, stressful delivery, perinatal asphyxia, meconium aspiration, or intraventricular hemorrhage) as well as infection, so a single measurement is not useful in diagnosing VS, as it is not sufficiently sensitive or specific. Its routine measurement can lead to unnecessary treatments, as one or more abnormal CRP values do not justify either the initiation or the maintenance of

empirical antibiotherapy in well-appearing neonates with negative blood/cerebrospinal fluid cultures (low positive predictive value). However, normal serial counts in the first 48 h of life make the presence of VS very unlikely (good negative predictive value).^{15,18,19}

- **Procalcitonin (PCT):** as it is also an inflammatory marker, its levels may also be affected by non-infectious perinatal mechanisms such as asphyxia, premature rupture of membranes, or pneumothorax. Its reported sensitivity for the detection of neonatal sepsis ranges between 72% and 79% and its reported specificity between 72% and 90%. It is also subject to physiological elevation in the first 24–48 h of life, which reduces its usefulness for diagnosing VS. Procalcitonin may be useful for assessing the course of the infection and determining the duration of antibiotic treatment.^{15,20}
- **Other reactants related to the inflammatory response associated with infection** are haptoglobin, fibrinogen, proteomic markers in amniotic fluid, inflammatory cytokines (including interleukin 6, interleukin 8, tumor necrosis factor α), or cell surface markers (including soluble CD14 subtype and neutrophil CD64), but, in general, none of them has a sufficient positive predictive value to be used as a diagnostic criterion for neonatal sepsis.

In summary, the combination and serial determination of reactants can improve diagnostic accuracy, although its use is not currently recommended for assessing the risk of sepsis in a neonate in good general health, as it leads to antibiotic overuse.^{15,21}

Management of the neonate at risk of/with suspected vertical sepsis

Management of neonates with gestational age ≥ 35 weeks²² (Fig. 3).

- **Asymptomatic neonate with risk factors.** Close monitoring of the infant along with the mother is recommended for the first 36–48 h post birth (especially the first 24 h) to rule out the presence of symptoms suggestive of infection. Risk factors include maternal fever $\geq 38^\circ\text{C}$ and/or inadequate IAP in a pregnant woman in whom it was indicated.
- **Neonate with symptoms suggestive of vs.** the recommended approach is collection of a blood sample for culture and initiation of standard empirical antibiotherapy (ampicillin + aminoglycoside), which should be stopped after 24–48 h if the cultures are negative and the infant is stable. If symptoms persist and no infectious cause is detected, alternative etiologies for the clinical presentation should be explored.
- **Neonate with respiratory symptoms.** It has been customary practice to treat all infants with respiratory distress at birth with antibiotics due to suspected sepsis/pneumonia, independently of the presence or absence of infection risk factors, even though it is known that most of these neonates have transient tachypnea. In this subset of patients, it is important to carefully consider infection risk factors and, above all, their clinical course in the first hours of life before choosing to initiate antibiotherapy.

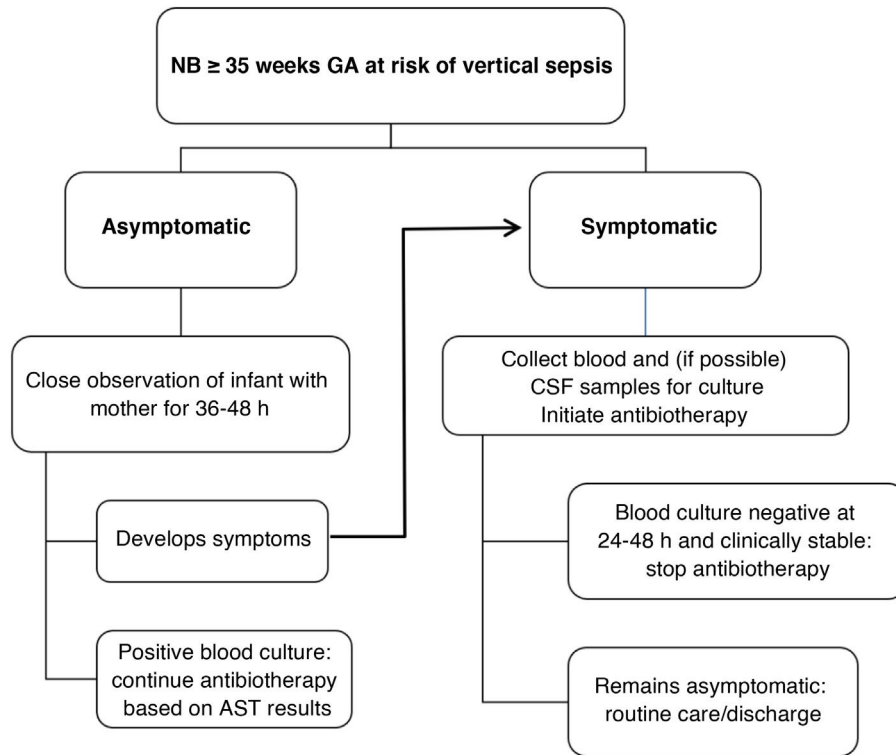


Figure 3 Algorithm for the management of neonates born at or after 35 weeks of gestation at risk of vertical sepsis. Abbreviations: AST, antimicrobial susceptibility testing; CSF, cerebrospinal fluid; GA, gestational age; h, hours; NB, newborn.

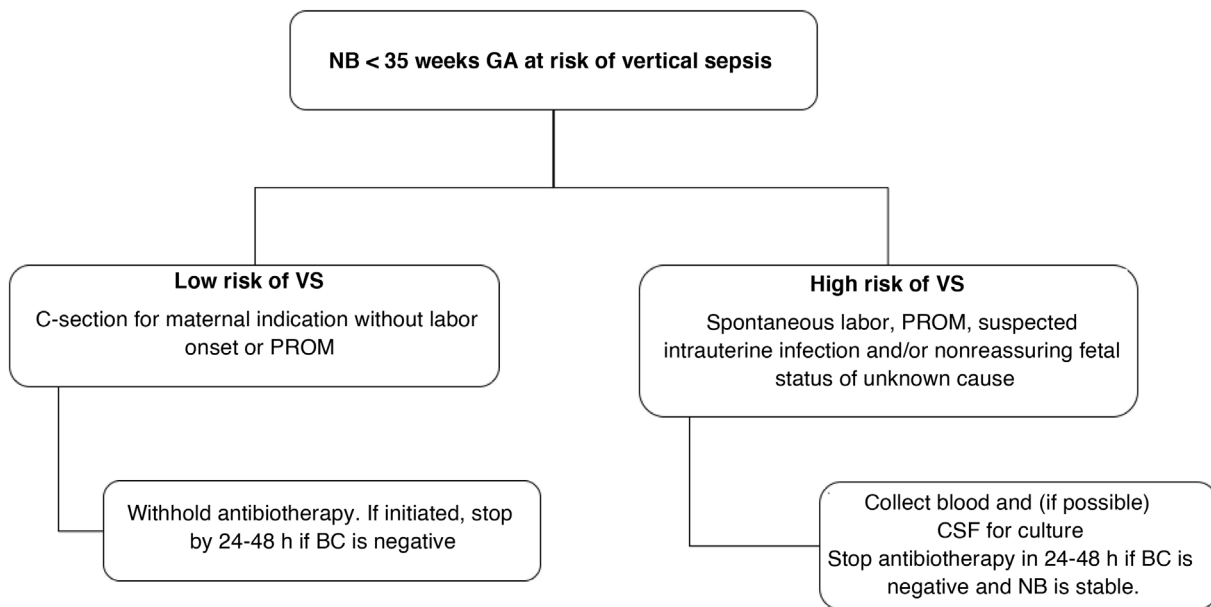


Figure 4 Algorithm for the management of neonates born before 35 weeks of gestation at risk of vertical sepsis. Abbreviations: BC, blood culture; CSF, cerebrospinal fluid; GA, gestational age; h, hours; NB, newborn; PROM, premature rupture of membranes; VS, vertical sepsis.

Management of neonates with gestational age < 35 weeks²³ (Fig. 4).

Since the risk of VS is inversely proportional to gestational age, many preterm infants receive antibiotics from birth and often for prolonged periods. However, it is possible to iden-

tify preterm deliveries carrying a low risk of sepsis in which initiation of empiric antibiotic therapy can be avoided as well as preterm infants whom, despite the presence of risk factors, are not going to develop vertical sepsis, in whom it is possible to stop the course of empirical antibiotic therapy early.

The strategies for stratifying the risk of infection in preterm neonates born before 35 weeks are:

- *Low risk vs.* Preterm infants born by cesarean section solely for maternal/fetal indications (preeclampsia, placental insufficiency, intrauterine growth restriction, etc), in absence of onset of labor or premature rupture of membranes (PROM). In these cases, the recommended approach is avoiding empirical antibiotherapy or, when it is initiated, withdrawing it within 24–48 h if the blood culture turns out negative.
- *High risk of vs.* Preterm birth due to cervical insufficiency, spontaneous preterm labor, PROM, suspected intrauterine infection and/or nonreassuring fetal status of unknown etiology. In these cases, performance of blood tests and blood cultures should be considered, and empirical antibiotherapy initiated; performance of lumbar puncture should be contemplated as indicated earlier in the text. If the blood culture is negative after 24–48 h, the discontinuation of antibiotic treatment will be considered based on the clinical course of the neonate.

Empirical and definitive treatment

Antibiotics are the drugs most frequently used inappropriately or unnecessarily in neonatal units. The lack of specific symptoms and diagnostic criteria for infection, together with the low positive predictive value of available biomarkers and the fear of sepsis, contribute to the excessive and unnecessary use of antibiotics.²⁴ The use of antibiotics in neonates contributes to the separation of the infant from their parents, delays breastfeeding initiation, alters the intestinal microbiota, and increases health care costs and antibiotic resistance. It has also been linked to a higher incidence of atopy, allergic disorders, asthma, and childhood obesity. In preterm infants, it can also lead to complications such as chronic lung disease, nosocomial sepsis, necrotizing enterocolitis, periventricular leukomalacia, severe retinopathy of prematurity, and poor long-term neurodevelopmental outcomes.²⁵

Empirical antibiotherapy should be initiated as soon as possible if sepsis is strongly suspected. A combination of ampicillin and an aminoglycoside (gentamicin, amikacin) is recommended to cover 83% of the pathogenic bacteria associated with vertical sepsis (GBS, *E coli*, *Enterococcus* spp and *L monocytogenes*).^{22,23,26} It should be noted that GBS currently remains sensitive to penicillin and ampicillin (100% of isolates according to data from the Castrillo Group), but *E coli* exhibits a high rate of resistance to ampicillin (75% of isolates), so an aminoglycoside must be added while awaiting the results of blood culture. The empirical use of third-generation cephalosporins (cefotaxime) or carbapenems is not recommended, as there is evidence that it promotes the development of antibiotic resistance and is associated with an increased risk of candidiasis, enterocolitis, and mortality in preterm infants.^{26,27} The empirical use of cefotaxime could be considered in cases of abnormal CSF analysis results and would be justified in the event of gram-negative bacterial growth in blood or CSF cultures (especially in very low birth weight infants), while awaiting susceptibility test results or in critically ill infants who

are not responding to first-line treatment (in this case, if the mother is colonized by a gram-negative beta-lactamase-producing bacterium, the use of meropenem would be recommended).

If active herpes simplex virus infection is suspected based on the obstetric history, the addition of intravenous acyclovir to the empirical antibiotic regimen should be considered.

Definitive targeted antibiotherapy will be based on antimicrobial susceptibility test results, always in monotherapy and using the narrowest-spectrum antibiotic to which the organism is susceptible (for example, penicillin in cases of sepsis not complicated by GBS).

There is no high-quality scientific evidence to establish the ideal duration of antibiotic treatment, but we offer the following broad recommendations based on the experience of the Grupo Castrillo Neonatal Network and the previous literature:

- *Duration of treatment for suspected vs.* To date, there is no unanimous agreement on the number of doses or days of empirical treatment in neonates with negative blood cultures and clinical improvement or symptoms attributable to another cause, partly due to differences in the processing of blood cultures. Most sources suggest discontinuation after 24–36 h if the blood culture is negative at that time.²⁴
- *Duration of treatment for clinical vs.* Despite negative blood culture results, if the clinical suspicion of infection persists and is accompanied by risk factors and abnormal blood test results, treatment may be prolonged for five days, and daily reevaluation of its necessity is recommended.^{12,28}
- *Duration of treatment for confirmed vs.* A maximum of seven days is recommended (for both gram-positive and gram-negative bacteria) as long as the response is favorable, adjusting treatment according to the susceptibility profile and always choosing the narrowest-spectrum option. In the case of sepsis caused by *S aureus* or *Listeria* spp, a minimum of 10 days is recommended. For sepsis associated with meningitis, the duration of antibiotherapy may extend to 14 days in the case of uncomplicated meningitis involving a gram-positive agent or to up to 21 total days or to 14 days after CSF cultures become negative in the case of uncomplicated meningitis involving a gram-negative agent.^{12,29}

Funding

This research did not receive any external funding.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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