The management of the late preterm and term newborn with early onset infection anno 2022

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Abstract

Early onset sepsis (EOS) is a common source of admission to a neonatal intensive care unit (NICU). Identifying children at risk for EOS remains essential but challenging because of aspecific clinical signs and poor predictive value of blood tests. Although the incidence of EOS has decreased over the past twenty years, primarily due to the introduction of intrapartum antibiotic prophylaxis, many children with low risk of EOS are evaluated and are treated unnecessarily. This leads to a separation of mother and child, an increase in health care costs, not to mention the side effects of antibiotics in future childhood. We conducted a review of the literature regarding the latest guidelines, inflammatory markers and tools that can help us in the evaluation and management of newborns at risk of EOS. The goal of this article is to discuss an evidence-based approach to the assessment and management of newborns > 35 weeks presenting with signs of possible EOS. An emerging trend is serial clinical examination which is promising to reduce newborn assessments and treatment. In all cases, EOS are unpredictable and clinical vigilance is essential over time.

Introduction

Early-onset sepsis (EOS), defined as sepsis with positive blood or cerebrospinal fluid culture occurring between birth and 72 hours of life occurs in 0.3-1/1000 infants born at ≥ 35 weeks' gestation (1-11).

EOS can result in severe outcome or death and remains a significant source of morbidity. Studies report a mortality rate of approximately 2-4% in newborns born ≥ 35 weeks (2,11). The incidence of EOS varies by country, local neonatal center, prophylactic antibiotic therapy practices, gestational age and the presence of symptoms or risk factors (2,8-11).

EOS is acquired before or during the delivery and results from a vertical transmission (12). The most common pathogens causing EOS among term and late-preterm are Group B *Streptococcus* (GBS) (40-45%) and *Escherichia coli* (10-15%). Other less common pathogens include Gram-positive cocci (predominantly group *Viridans streptococci* and *Enteroccoccus spp.*), Gram-negative pathogens (5%), *Staphylococcus aureus* (≈3-4%) and *Listeria monocytogenes* (≈1-2%) (1-4,7,12,14).

Intrapartum antibiotic prophylaxis (IAP) in mothers with GBS colonization reduces neonatal EOS due to GBS significantly but not due to *E. coli* (7).

Peripartum risk factors (table 1) account for 10-20% of deliveries and are similar for *E. coli* and GBS or other common bacteria responsible for EOS (1-3,7,8,12-15).

Clinical manifestation of EOS is often non-specific, subtle and may mimic noninfectious disease (12). Recent studies in the US reported that 13% of all term newborns were evaluated for EOS using the CDC guidelines of 2010 and that 11% of them were treated empirically with antibiotics while only 0.04% of the newborns in the study had a blood culture confirmed infection (16). Even if we are all aware of the high risk of mortality and morbidity associated with EOS, recent research has shown the negative effects of unnecessary antibiotherapy such as the increase of antibiotic resistance or the disruption of the neonatal microbiome that may lead to obesity, asthma, autoimmune disease, inflammatory bowel disease and neurological disorders (12,17). Inaccurate EOS evaluation or empirical antibiotherapy also leads to maternal-infant separation with negative effects on bonding and breastfeeding with

Table 1: Risk factors of EOS

- Maternal colonization with GBS
- Prolonged rupture of membranes (>18h before delivery)
- Chorioamnionitis *
- Prematurity (<37 gestational weeks)
- Maternal GBS bacteriuria during the current pregnancy
- The history of a newborn with invasive GBS disease
- Inadequate intrapartum antibiotic prophylaxis **

* Now called maternal intra-amniotic infection according to the new recommendations by the American College of Obstetricians and Gynecologists (ACOG) in 2020). Suspected intra-amniotic infection based on ACOG is defined as "maternal intrapartum fever > 39°C or maternal temperature between 38°C and 38.9°C in combination with one or more criteria as well as maternal leukocytosis, purulent cervical drainage, or fetal tachycardia") and occurs in 1-10% of full term births (13).

** The adequate IAP is penicillin G, ampicillin or cefazolin, and administration should be done more than 4H before delivery. Vancomycin or clindamycin used in high risk cases for penicillin anaphylaxis is not adequate IAP. These antibiotics can have some protection but are not the first recommended because not enough evidence of protection. They are considered inadequate, as is the dose is done <4h before delivery (13).

increased formula supplementation, frequent blood samples and insertion of intravenous lines, potential antibiotic resistance, extension of hospital stay and costs that could have been avoided (1,2,6,10,15-17).

Diagnosis

Clinical signs and symptoms

According to the literature, most newborns with EOS become symptomatic within 12 to 24 hours of life (14). Newborns have a low risk of developing EOS if they are asymptomatic at birth and have an even lower risk if adequate intrapartum antibiotic prophylaxis was given during labor (1,4,10). Clinical evaluation is the strongest predictor of EOS.

The initial symptoms of EOS can be focal signs of infection or unspecific symptoms (table 2) like tachypnea with retractions, nasal flaring or grunting mimicking a transient tachypnea of the newborn, which makes it very hard for physicians to withhold the beginning of antibiotherapy in some situations (1,6,7,10,13,15). In borderline situations, it is essential to reevaluate the newborn and to eventually confirm the clinical improvement and that the antibiotics are not necessary.

Table 2. Clinical signs of sepsis

Neurological signs and behavior	Temperature instability	Respiratory instability	Hemodynamic instability
Lethargy Altered muscle tone (floppy baby) Irritability, bulging fontanel Seizures, neonatal encephalopathy Poor feeding	Fever Hypothermia	Signs of respiratory distress with polypnea, grunting, apnea Need of supplemental oxygen Non-invasive support (e.g. CPAP) or invasive support with mechanical ventilation Persistant pulmonary hypertension	Tachycardia, Bradycardia Hypotension Prolonged blood capillary refill time Blood pressure support (e.g. inotropic agents)

Blood tests

Common diagnostic tests such as C-reactive protein (CRP) and complete blood count have been used routinely in the evaluation of EOS but have poor sensitivity and low predictive value in case of newborn infants (1,7,10,13,15).

First of all, abnormal white blood cell (WBC) count, neutropenia in particular, has been highlighted in newborns who were exposed in utero to an inflammatory process (e.g. in case of premature rupture of membranes) instead of an infectious process but also in cases of maternal preeclampsia or placenta insufficiency while thrombocytopenia is not an early sign of infection in a neonate (2,12,18). Table 3 shows upper and lower limits of neutrophils count (19). Immature to total neutrophil count is the hematologic marker that has the highest positive predictive value (15,17). The values of WBC will also vary naturally during the first 12 hours of life (12).

With regards to CRP, its increase will appear only after hepatic synthesis has started and may increase in response to various stimuli. Therefore CRP should not be tested or at least, in case of normal value, not be taken into account in the early process of a potential infectious disease (12). If tested, the predictive value is improved if it is obtained after 4 hours of life (according to several studies, at least 6 to 12 hours of life) (15).

Both blood markers have a high negative predictive value. Even in the presence of clinical symptoms and risk factors, serial negative CRPs taken after 12 hours of life rules out sepsis. Thus, serial measurements are more informative than single values but should be reserved for symptomatic newborns. Serial measurements of normal values can reassure the physician to avoid starting or to allow for the discontinuation of the antibiotics in case of therapy (2,12,17).

Some other inflammatory markers (such as procalcitonin) have been suggested to help physicians to determine whether or not an infectious process is in progress. The use of IL-8, a proinflammatory cytokine which rises earlier than CRP in the course of neonatal infection, has proven added value in the diagnosis and treatment of neonatal EOS, but is of no clinical value at this moment in Belgium due to the lack of reimbursement (20).

Table 3. Upper and lower limits of neutrophils/mm3 over time according the study report by Schmutz and al. (19)

Timing of neutrophil count	Neutrophil count (x10^9/L)	
	Gestation 28-36 weeks	Gestation > 36 weeks
at delivery	1.0 - 10.5	3.5 - 18
at 6-8 h after birth	3.5 - 25	7.5 - 28.5
at 72h-240 h after birth	0.8 - 12.5	2.7 - 13

* The results of this study showed higher upper limits of neutrophils counts compared to Manroe's traditional chart in 1979 or Mouzinho report in 1994 (chart for <36 weeks) but similar upper limit value compared to Carballo's study in high-altitude. The difference between Manroe and this study can be possible explain by modern method of counting of neutrophils (old vs new) and variations in altitude.

Culture

Blood culture or cerebrospinal fluid (CSF) culture is the confirmatory diagnostic tool. Generally, a minimum of 1ml of blood is required in a pediatric blood culture bottle to increase sensitivity and ideally 2 samples (from 2 different sites) should be taken (2,12,17). If the newborn has a central catheter, one of the blood samples should be taken from the vascular catheter (12). In case of intrapartum antibiotic prophylaxis (IAP) the density of pathogens in the blood are decreased so a volume of >1 ml blood might increase the sensitivity (21).

According to several studies, there is no effect of IAP on the timing of blood culture positivity, with a median time to positivity < 24 hours (2). There is no need for an anaerobic culture bottle.

Urine culture is not indicated and gastric aspirates or body surfaces cultures are not recommended because of sub-optimal sensitivity and specificity and because of their poor predictive value for infection (12,15).

Placental culture will inform the physician to which bacteria the newborn has been exposed in utero, but will not necessarily indicate a true infection. Acute or chronic intrauterine inflammation might be highlighted by the anatomopathological analysis of the placenta (12).

Management of the newborn > 35 weeks

Approach for the symptomatic newborn

In case of clinical signs of sepsis, it is necessary to start a full diagnostic evaluation regardless of risk factors or IAP (15). It has been demonstrated that newborns exposed to IAP with confirmed EOS were more often symptomatic at birth than unexposed newborns (4).

Full diagnostic evaluation should include a full blood cell count, CRP and a blood culture (min 1ml or 2ml if IAP). A lumbar puncture (LP) should be done if the newborn has signs suggesting meningitis or if there is a strong suspicion or proven sepsis, but only if the child is stable enough to tolerate the procedure (2,22). A repeat LP should be done after 24-48 h of therapy if CSF culture is positive or if there is no response to the initiated treatment. In case of respiratory symptoms, a chest X-ray should be done and an endotracheal culture should be taken in case of intubation even after initiation of antimicrobial therapy. All cultures should preferably be sampled before antibiotherapy is initiated, but antibiotics should never be delayed in case of difficult sample (e.g. septic shock patient).

In case of an isolated clinical sign (e.g. isolated tachypnea in the first hour of life, isolated temperature after a long labor, epidural anesthesia, isolated maternal fever,…), diagnostic evaluation can be postponed but a clinical re-evaluation must be done in the first 1 or 2 hours of life and midwifes and/

or nurses should be fully informed and aware of signs that would need an earlier medical intervention.

Following the diagnostic evaluation, empirical antibiotherapy (ampicillin/amoxicillin or penicillin + aminoglycoside) should be started with weight and gestational age adjusted doses (13). Third or fourth-generation of cephalosporin drugs are reserved for suspected meningitis. In case of rapid recovery or absence of arguments for a sepsis it may be possible to stop antibiotics. Serial evaluation of biomarkers like CRP and WBC counts may help physicians to decide how long antibiotherapy should be continued.

Two negative CRPs (< 10 mg/L) at an interval of at least 24h rule out sepsis with a specificity of 99.7% and should be a strong argument for the discontinuation of the antibiotics unless there is evidence of site-specific infection (2,17).

It would be reasonable to perform 2 serial CRP levels at 12h and at the time of the aminoglycoside trough level. When the 2 serial CRP levels are below 10 mg/L (negative) and blood culture remains negative after 24h incubation, the antimicrobial therapy can be stopped when the clinical condition is stable or improved. This would be probably in more than 50% of the neonates with suspected neonatal EOS. A recent study showed that time of positivity of blood culture was < 24 hours in most children and occasionally 36-48h (23). So in case of absence of positive blood culture, physicians should consider stopping antibiotherapy after 24 and 36h if there is no other argument for sepsis. However, a positive CRP will not confirm the presence of an infection and should not be an argument to extend the duration of antibiotherapy in a well-appearing newborn with negative cultures whatever the risk factors that had been highlighted (17). In these neonates with "clinical" infection a switch after 48 hours of IV antimicrobial therapy to oral therapy has not only been proven to be safe, it also decreases hospital stay and increases breastfeeding success because the neonate will not be separated from the mother (24,25). In these children oral amoxicillin instead of ampicillin is the first choice due to its high oral bioavailability. The duration of antibiotherapy varies between 5 and 21 days (table 4).

Table 4. Duration of antibiotherapy

	Duration of antibiotherapy
Proven sepsis*	5 to 10 days
Gram positive meningitis	14 days
Gram negative meningitis	21 days

*In case of "proven" sepsis, duration of antibiotherapy will depend on the results of the cultures and on the clinical evolution of the infant. Usually in case of positive blood culture, antibiotherapy is continued for a period of 5 to 10 days pending the clinical and CRP evolution. Indeed, in case of uncomplicated sepsis, when CRP becomes negative (e.g. at day 5) and the patient's clinical condition is improved, antimicrobial therapy can be stopped without the risk of relapse (30).

Approach for the asymptomatic newborn

The management approach of an asymptomatic newborn is highly challenging. In the words of Richard A. Polin in 2021, "early onset sepsis: finding a needle in a haystack" (9). Indeed, the management of these babies remains controversial and heterogenous (13,14).

Several guidelines have been published in the last twenty years by various committees worldwide (e.g. American Academy of Pediatrics (AAP), United States Center for Disease Control and Prevention (CDC), National Institute for Health and Clinical Excellence from United Kingdom (NICE)) in order to evaluate treatment and generate algorithms for managing newborns with risk factors or clinical symptoms (14,22). Nevertheless, we should not forget that even newborns with no risk factors may develop EOS (e.g. GBS EOS can occur with negative GBS carriage). We will need to consider the balance of risk and benefit before starting an empiric antibiotherapy.

We have several options for assessing the risk of EOS and evaluating the need for a diagnostic evaluation and further for an eventual treatment:

Categorical risk assessment: this algorithm is based only on standard perinatal risk factors to identify babies at high risk of EOS. This approach was recommended by the first consensus and guideline published in 1996 by CDC. In 2014 a Belgian guideline was published (15). With these guidelines, any well-appearing newborn from a mother with suspected chorioamnionitis would receive an empirical treatment until proven otherwise, and those with prolonged rupture of membranes (PROM) with inadequate IAP would be subjected to laboratory evaluations. With the low risk of EOS, the estimated number needed to treat (NNT) well-appearing babies born to mothers with suspected chorioamnionitis, is > 450 (16,26). Unnecessary evaluations and empiric treatment of well-appearing newborns with low risk resulting from these guidelines make this approach outdated (13,14,27).

A. Multivariate risk assessment: the neonatal EOS calculator is a tool whose purpose is to reduce laboratory testing or empiric treatment by helping physicians to evaluate the risk of EOS. This free online calculator (https://neonatalsepsiscalculator.kaiserpermanente.org/) was developed by Puopolo and Escobar at Kaiser Permanente in California in 2012 and was then modified over time. This tool, based on the incidence of EOS in each institution, gestational age of the newborn, highest maternal antepartum temperature, time from membrane rupture to delivery, maternal GBS status and the type of intrapartum antibiotherapy, estimates the baby's individual risk of EOS caused by any pathogen in the first 24 hours of life for babies of more than 34 weeks.

Depending on the clinical status of the newborn, an evaluation of the risk of EOS is reported and a clinical recommendation is suggested. The advantage of this tool is that the first evaluation only includes objective data and not a clinical diagnosis of maternal chorioamnionitis (2).

A recent meta-analysis conducted by Achten et al. (2019) showed that there was a reduction in laboratory testing and empirical treatment after the implementation of the EOS calculator in comparison with conventional strategies (6). Nevertheless, rates of missed cases of EOS were comparable to those that were observed when categorical risk assessment is used.

According to the main study on the use of the EOS calculator, "2.6% of all term and late-preterm neonates received antibiotics in the first 24 hours of life" (11).

However, with the use of the calculator, all patients classified in the category " clinical illness" are indicated to receive antibiotherapy. The calculator could still overestimate EOS, because simply having non-invasive CPAP breathing support without oxygen falls into this category. E.g. a baby born at 39 week' gestation supported with non-invasive CPAP because of transient tachypnea, does not necessarily need antibiotic therapy but the calculator will recommend it based on the "clinical illness". This child could very well be monitored clinically in the NICU and the need for antibiotic therapy could be reassessed within 2 hours of admission.

Literature has shown that implementation of the calculator in units reduced antimicrobial use around 50% without an increase in undiagnosed EOS cases (5,6). However, there are no specific data to evaluate if this approach would be safe in Belgium.

It should be noted that a selected American population was used to develop the mathematical model for prediction of the calculator. Since the local incidence will be different for other populations and will influence the final score and the threshold to treat (the probability of missing a case will increase if we use a lower EOS incidence) and since the GBS screening policy and thus the method of observation time of newborns may be different elsewhere, generalizing this tool to other health care settings outside the US or to at-risk populations with higher EOS local incidence would probably not be recommended (5,6,14).

The calculator is thus helpful but it does not replace the clinician and can still result in over-treatment. Clinical monitoring remains essential even when the baby is allocated in routine care (5).

Studies comparing the calculator method and repeated clinical examinations should be carried out (currently a multicenter prospective Italian study is underway).

B. Serial clinical examinations: Since the vast majority of infants developing EOS will be symptomatic within the first 24 hours of life, serial clinical examinations have become an emerging trend in the management of well-appearing newborns. This strategy, regardless of any risk factor, results in the evaluation and potentially the treatment of newborns who develop signs of illness during the first 48h of life (2,13).

Several studies reported that serial physical examinations every 4 to 6 hours through 48 hours of age lead to a significant decrease in the use of antibiotherapy, laboratory tests and blood cultures and this without a delay in the initiation of antibiotic treatment in case of infection (1,2,4,10,14, 28). Nevertheless, this approach requires a lot of resources: sufficient medical and trained nursing staff, clear protocols with optimal assessment (structured vital signs – heart rate, respiratory rate, temperature, protocols that will define which parameters and which abnormal signs require assessment by a physician). The decision to start antibiotics will be left to the discretion of the physician. Much larger studies will be needed to assess safety and use in comparison with the EOS calculator.

Conclusion

EOS is rare but because of the potential consequences of incorrect diagnosis and treatment, it is often over diagnosed and over treated. Clinical signs are aspecific and can mimic another benign illness. Laboratory tests lack specificity and sensitivity. It is important to keep in mind that antibiotic treatment will save a newborn's life in case of sepsis but will have long-term side-effects in case of unnecessary administration. Therefore, physicians will have to consider the risk/benefit balance when initiating antibiotherapy and should ask themselves whether it is necessary to continue the antibiotics when sepsis is not confirmed.

In the same way, unnecessary evaluations will result in parental concerns, mother-infant separation with parental anxiety, delayed breastfeeding, higher financial costs and longer hospital stay.

Different approaches are possible (categorical risk assessment, sepsis calculator or serial clinical examinations). Each approach has its advantages and disadvantages, and to date none can ensure perfect case detection. Clinical vigilance is essential with repeated physical evaluations leading to the best risk/benefit balance. Large-scale studies comparing different strategies are recommended for better practice and avoiding unnecessary antibiotics.

Ultimately, we can say that not all EOS are predictable. Thus, clinical evaluation remains an essential part of the early diagnosis (27,28).

Conflict of interest

The authors have no conflict of interest to declare with regard to the subject discussed in this manuscript.

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