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Recognising early onset neonatal sepsis: an essential step in appropriate antimicrobial use

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Summary Early diagnosis and timely treatment of early onset neonatal sepsis (EOS) are essential to prevent life threatening complications. Subtle, nonspecific clinical presentation and low predictive values of biomarkers complicate early diagnosis. This uncertainty commonly results in unnecessary and prolonged empiric antibiotic treatment. Annually, approximately 395,000 neonates (7.9% of live term births) are treated for suspected EOS in the European Union, while the incidence of proven EOS varies between 0.01 and 0.53 per 1000 live births. Adherence to guidelines for the management of suspicion of EOS is poor. Pragmatic approaches to minimise overtreatment in neonates with suspected EOS, using combined stratified risk algorithms, based on maternal and perinatal risk factors, clinical characteristics of the neonate and sequential biomarkers are promising.

Background

Despite a decreasing incidence over the past decades, early onset neonatal sepsis (EOS) remains a leading cause of neonatal morbidity and mortality worldwide.[1,2] Proven EOS has mortality rates as high as 30% in high-income countries, and up to 60% in low-income countries.[3—5] EOS is generally defined as the onset of symptoms of infection occurring within 72 h after birth, and is commonly acquired by vertical transmission by contaminated amniotic fluid or during vaginal delivery from bacteria in the maternal genital tract. The majority of infections are caused by group B streptococcus (GBS), *Escherichia coli* (*E. coli*) and coagulase-negative staphylococci (CoNS),

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Table 1 Most common causative organisms of EOS.[6–10]

Pathogen	Percentage of positive blood cultures in EOS	
	UK	USA
Gram-positive		
Group B streptococcus (GBS)	58%	43%
Coagulase-negative staphylococci (CoNS) *frequently considered as contaminant*	20%	24%
Gram-negative		
Escherichia coli (*E. coli*)	18%	29%

although CoNS is frequently considered to be a skin-derived contaminant (Table 1).[6–10]

Early diagnosis and treatment of EOS is essential to prevent severe and life threatening complications.[11] The timely identification of neonates with infection is a daily challenge for paediatricians worldwide. Symptoms of EOS such as respiratory distress, hypo- or hyperthermia or feeding intolerance are non-specific as these symptoms are also often observed in neonates without infection. In addition, there is a lack of highly sensitive and specific diagnostic tools: conventional laboratory parameters as C reactive protein (CRP), and white blood cell count (WBC) are non-specific, and not adequately sensitive.

The incidence of proven EOS in high-income countries varies from 0.01 per 1000 to 0.53 per 1000 live births in Europe and 0.67 per 1000 live births in Australia.[12] In low-income countries the incidence of EOS varies from 0.01 to 3.06 per 1000 live births.[3] The lack of consensus in existing guidelines for management of suspected EOS,[13] and a low threshold for paediatricians to evaluate and treat a neonate with suspected EOS, lead to unnecessary treatment and hospitalization of estimated 395,000 neonates (7.9% of all term birth) in the European Union (EU) annually (Fig. 1).[14] Unnecessary treatment and hospitalization is undesirable because of the risk of promoting multidrug resistant bacteria and interference of mother-infant bonding.[15,16] In addition, evidence is accumulating that antibiotic treatment early in life disturbs the microbial flora colonizing the neonate, and is associated with important health problems such as eczema, allergies, and inflammatory bowel diseases in later life.[17–19] Similarly important are the financial costs and use of resources due to unnecessary hospitalization. Overtreatment could be reduced if better diagnostic tools and algorithms with proven safety would be available (Fig. 1).[20]

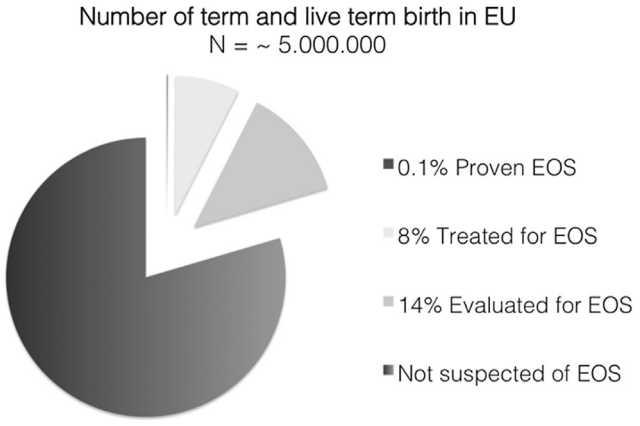

Figure 1 Estimation of the proportion of babies suspected and proven to have EOS.[14]

Current management of suspicion of EOS

Assessment when to start antibiotic therapy

Clinical symptoms

Symptoms of suspected EOS, including respiratory distress, tachy- or bradycardia, poor perfusion, hypo- or hyperthermia, irritability/lethargy and feeding intolerance/vomiting are non-specific. Nevertheless, all current guidelines recommend starting antibiotic therapy in term and near term neonates with clinical signs of EOS.[21–25] In the absence of clinical symptoms, the decision to start antibiotic therapy is based on maternal and/or perinatal risk factors and/or laboratory investigations.[21–25]

Risk factors

Important perinatal risk altering factors for EOS are prematurity (<37 weeks gestational age), low birth weight, prolonged rupture of membranes (≥18 h), intrapartum fever and GBS colonization.[8,9,26,27] Recommendations by the guidelines regarding perinatal risk factors differ from *not to treat risk factors alone, always treat, treat only in case of abnormal laboratory results, or to treat if there are ≥2 risk factors*.[21–25] A cohort study published in 2000 identified intrapartum fever and GBS colonization as the most important maternal risk factors for EOS.[28] However, using only maternal intrapartum fever as a risk factor for EOS is nowadays complicated by the widespread use of epidural analgesia causing fever in around 20% of the mothers. Indeed, neonates of women exposed to epidural analgesia are more often evaluated for sepsis and treated with antibiotics.[29]

The impact of maternal GBS colonization as a risk factor for EOS has been reduced by the implementation of national guidelines for GBS prophylaxis in pregnant women during the last 25 years. Since the first implementation of these guidelines in the USA, the worldwide incidence of GBS EOS decreased significantly with reductions varying between 50% and 71% in different countries.[9,30,31] Surprisingly, during more recent years an increase of the incidence of GBS EOS has been reported in the United Kingdom, the United States and the Netherlands. These increases are, as yet, unexplained.[32]

A common reason for the administration of intrapartum antibiotics is suspected chorioamnionitis (46%); usually defined as maternal fever and fetal tachycardia, independent of placenta pathology analysis. All current national guidelines have different specific recommendations for the management of neonates born to mothers with chorioamnionitis, varying from *observation*, always *treat if chorioamnionitis is present*, to *treat in case of abnormal laboratory results*.[21–25] Accordingly, the results of an international survey among 439 physicians from high-