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Immunoinflammatory prognostic markers of early-onset neonatal sepsis in critically ill preterm newborns

Marcadores imunoinflamatórios para prognóstico de sepse neonatal precoce no recém-nascido pré-termo criticamente enfermo

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It is challenging to determine the relationship between inflammatory and oxidative markers and the severity of sepsis in preterm neonates. This is especially true considering the high mortality caused either directly or indirectly by the pathogen and the classical immunoinflammatory multiorganic response, which causes significant delays in the neurodevelopment outcomes. The complications of neonatal sepsis include severe intraventricular hemorrhage (grades III and IV) with or without post-hemorrhagic dilation and periventricular leukomalacia.⁽¹⁻³⁾ TNF- α is an early neonatal sepsis marker, and its relationship with septic shock and diffuse tissue damage is well-defined in neonatology.⁽⁴⁾ Cytokines, especially interleukin-6, are produced by a number of cells and are highly sensitive markers of early-onset neonatal sepsis in association with other immune-inflammatory markers, such as TNF- α , interleukin-8, procalcitonin and C-reactive protein.⁽⁵⁾

However, several peripartum conditions promote a balance of proinflammatory and anti-inflammatory events, affecting the cytokine levels in both: blood and cord blood samples. The multiple-hits theory describes perinatal inflammation as a cause and/or consequence of future impairment and poor prognosis in critically ill patients.⁽⁶⁾ Fetal inflammatory response is a frequent cause of preterm delivery; indeed, it is estimated that 40% of preterm deliveries are associated with intra-uterine infection.⁽⁷⁾ Additionally, preterm delivery is associated with immunological immaturity, rendering the preterm infant particularly vulnerable to early neonatal sepsis.⁽⁸⁾

In this issue of the Brazilian Journal of Intensive Care, Valerio et al. conclude that thiobarbituric acid reactive substances (TBARS) and IL-6 have a mild to moderate correlation with the SNAPPE-II severity scores but not mortality. The authors suggest that these molecules may represent early diagnostic markers of neonatal sepsis but they aren't good prognostic markers or good predictors of infection as a direct cause of death.⁽⁹⁾ The data published by Valerio et al. are interesting and deserve further investigation in the future.⁽⁹⁾ Several studies indicate that fetal inflammatory response preceding early delivery and increased fetal circulating cytokines are related to an increased risk of neonatal morbidities that diminish the short- and long-term prognosis of neonates, such as perinatal asphyxia, retinopathy of prematurity, bronchopulmonary dysplasia, white matter injury and cerebral palsy.⁽¹⁰⁻¹³⁾

Recently, we investigated the association between increased cytokine levels and retinopathy in seventy-four very low birth weight preterm infants with clinical criteria consistent with early infection; cytokines were assessed within

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the first three days of life. IL-6 > 357 pg/mL, IL-8 >216 pg/mL and TNF- α > 245 pg/mL were significantly associated with the development of retinopathy of prematurity.⁽¹⁴⁾ Maternal chorioamnionitis, even when controlled for gestational age, gender, birth weight and maternal use of steroids and antibiotics, increases the risk of cerebral hemorrhage and retinopathy of prematurity.⁽¹⁵⁾ In a two-year cohort follow-up of very low birth weight preterm newborns, we found that the severity of early-life inflammatory response, as measured by the levels of

proinflammatory cytokines, was associated with poorer neurodevelopment outcome at two years corrected age.⁽¹⁶⁾

It is fundamental to understand the immune-inflammatory response secondary to neonatal sepsis and to describe a set of markers that can predict impairments. These markers should be assessed in future multicenter trials. It is currently unclear whether inflammatory response that begins in utero is the major factor responsible for the unfavorable events that are common in preterm infants.

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