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Review Article

Sepsis screen in neonates: How relevant?

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ABSTRACT

The search of an ideal sepsis marker is still continuing in spite of the fact that the diagnostic armamentarium is inundated with many hematological markers, acute phase reactants, cytokines, chemokines, genomics, proteomics, and new emerging molecular technique. Blood culture is treated as gold standard for the diagnosis of sepsis, but it takes about 24–48 hrs for microbial isolation. Thus, an ideal sepsis marker is essential to guide the treatment in case of sepsis. None of the sepsis markers alone or in combination have the characteristics of an ideal sepsis marker.

1. Burden of the disease

Sepsis is the second commonest cause of newborn mortality, contributing to 27.5% of all newborn deaths. Pneumonia, sepsis, and meningitis cumulatively contribute to 22.5% of newborn deaths, while tetanus and diarrhea contribute to 2.5% each. Studies from developing countries, based on population, have found infection rates in the range of 49–170 per 1000 live births.[1]

In India, the incidence of neonatal sepsis as per the data from National Neonatal Perinatal Database (NNPD, 2002–03) is 30 per 1000 live births.[2]

The two forms of disease, early-onset and late-onset, are a part of systemic bacterial sepsis during the first month of life. Early-onset disease usually manifests as a fulminant, systemic illness during the first 24 hours of life, with the large majority of other cases manifesting on the second day of life. Late-onset disease has been defined as occurring after 72 hours to 6 days of life. Bacteria accountable for late-onset sepsis (LOS) and meningitis are acquired from the maternal genital tract and organisms acquired after birth are from human contacts or, occasionally, from contaminated hospital equipment or materials, where protracted intensive care is required for such neonates.[3]

In a retrospective study done by Venkataseshan et al., a total of 34,362 neonates were born during the study period from 1995 to 2006. Of these, 11,981 (35%) were preterm (<37 completed weeks of gestation). Blood culture was positive in 1491 neonates; 1328 (89%) neonates were bacterial and were labeled as proven bacterial sepsis (38.6 per 1000 live births) while the remaining 11% neonates had fungal sepsis. *Klebsiella pneumoniae* and carbohydrate nonfermenting Gram-negative bacilli (NFGNB) were the most common organisms causing early-onset sepsis (EOS) whereas *Staphylococcus aureus* was the most common isolate from LOS.[4]

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2. Ideal infection marker characteristics

Regarding an ideal infection marker, the marker should be detectable in a small amount of blood; the compound used should be stable biochemically; the transport need should be minimal; the process used should be fast and easy; the procedure should be automated. The test analysis can be undertaken by less skilled laboratory workers. In order to make a test routine procedure, it should incur low cost. For an ideal sepsis marker, the sensitivity and negative predictive value should be very high (about 100%). The specificity and positive predictive value should be more than 85%. The sepsis marker should have clearly defined value to distinguish from noninfected cases. The test would be more helpful if it can distinguish the causative organisms like bacterial, fungal, or viral. The marker should be able to predict the progression of the disease.[5]

3. Different markers of sepsis

Although blood culture is the gold standard for the diagnosis of sepsis, it takes more than 48 hours in yielding a result. There are many other sepsis markers, which help to institute early therapy. The different markers are total leukocyte count (TLC), absolute neutrophil count (ANC), immature to total neutrophil ratio (IT ratio), platelet count, acute phase reactant like C-reactive protein (CRP), procalcitonin, micro-erythrocyte sedimentation rate (ESR), IL1, IL6, CD11b, and CD64.

4. Total leukocyte count

The utility of blood cultures, the gold standard, is confined by the time required to isolate the organism and by problems in getting adequate blood volume to reliably isolate organisms. The complete blood cell (CBC) count is a rapid, cheap, and easily available diagnostic test.

Hornik et al., in their study of the largest series of CBC counts in neonates with early-onset sepsis, found that the leukopenia (<5000/cmm) had poor sensitivity (17.7%), positive likelihood ratio (4.7), and negative likelihood ratio (0.9) with high specificity (96.3%).[6] Similarly, Spector et al. in their study on newborns of early-onset sepsis observed the poor sensitivity of leukopenia (<5000/cmm) (32%). The same was observed by Anwer et al. and Ottolini et al. in their study on early-onset sepsis of newborns.[7–9]

Philips et al. (1975–80) in their study observed that leukocyte count <5000/cmm in late-onset sepsis of all infants had 33% sensitivity, 90% specificity, 57% positive predictive value (PPV), 3.3 positive likelihood ratio (PLR), and 0.7 negative likelihood ratio (NLR). Similarly, leukocyte count >20,000/cmm had 25% sensitivity, 88% specificity, 50% positive predictive value (PPV), 2.1 positive likelihood ratio (PLR), and 0.9 negative likelihood ratio (NLR).[10]

Gonzalez et al. (1986–88) in their study found that leukocyte count >9000/cmm in late-onset sepsis had 74% sensitivity, 56% specificity, 13% PPV, 96% negative predictive value (NPV), 1.7 PLR, and 0.6 NLR.[11]

The same was observed by Fanaroff et al. (1988–91) whose study showed that leukocyte count >20,000/cmm in late-onset sepsis of VLBW babies had poor sensitivity (18%) and poor PPV (15%).[12]

DaSilva et al. (1994) in their study had similar observation that leukocyte count <5000/cmm or >20,000/cmm in late-onset sepsis of all infants had poor sensitivity (36%), poor PPV (29%), 80% specificity, 84% NPV, 1.8 PLR, and 0.8 NLR.[13]

Hornik et al. (1996–2009) obtained complete blood count (CBC) and culture data from infants having late-onset sepsis admitted to 293 NICUs in the United States managed by the Pediatrix Medical Group. The mean white blood cell count (WBC) was 15,287/cmm (5th, 95th percentile: 4200/cmm, 33,800/cmm) and 15,214/cmm (5th, 95th percentile: 5400/cmm, 32,400/cmm) for positive and negative culture results, respectively ($P = 0.48$). For infants with positive cultures and values for all CBC indices, 14.4% (1219/8472) were noted to have completely ''normal'' CBC indices (WBC count 5000/cmm–19,000/cmm, ANC ≥1500/cmm, I/T ratio <0.2, and platelet count 150,000/cmm–399,999/cmm). High WBC counts were associated with statistically significant odds ratios for infection observed from the 17th to the 20th vintile, corresponding to a WBC count >20,300/cmm. Low WBC counts <6800/cmm (first and second vintile) were also associated with increasing odds of infection. Among blood culture positive late-onset sepses, only 7% had leukopenia (<5000/cmm), 70% had normal leukocyte count (5000–19,999/cmm), and only 23% had leukocytosis (≥20,000/cmm).

Specificity was highest for white blood cell counts <1000/cmm and >50,000/cmm (>99%). Positive likelihood ratios were highest for white blood cell counts <1000/cmm. In the largest study of CBC counts in infants with LOS admitted to the NICU, there was increased odds of infection for high (>20,300/cmm) and low leukocyte counts (<6800/cmm), high ANC (>17,670/cmm), high IT ratio (>0.2), and low platelet count (<130,000/cmm). However, none of these complete blood count (CBC) index cut-offs were associated with high sensitivity or positive likelihood ratio.[6]Similarly, Squire et al. in their study found that 27% of culture positive sepsis had leukopenia (TLC < 5000/cmm) and only 5% of culture positive sepsis had leukocytosis.[14]

King et al. in their study observed that total leukocyte count <5000/cmm in blood culture positive sepsis had 44% sensitivity, 96% specificity, 37% PPV, 97% NPV, 11.81 positive likelihood ratio, and 0.58 negative likelihood ratio.[15]

Thus, different studies have shown that leukopenia and leukocytosis have poor sensitivity and positive predictive value as a sepsis marker. The diagnostic ability of leukopenia in early-onset and late-onset sepses in different studies is shown in Tables 1 and 2, respectively.

5. Absolute neutrophil count (ANC)

Manroe et al. showed that in their population, the lower limit for ANC, for example, was 1800/mm^3 at birth, rose to 7200/mm^3 at 12 hours of age, and then fell to 1800/mm^3 by 72 hours of age.[16]

Various studies done for determining the correlation of ANC with sepsis have shown poor sensitivity and PPV.

Gonzalez et al. (1986–88) in their study observed that ANC >5000/cmm in late-onset sepsis had 67% sensitivity, 65%