Biomarkers for Late-Onset Neonatal Sepsis: Cytokines and Beyond

Pak C. Ng, MD, FRCPCH*, Hugh S. Lam, MRCPCH

KEYWORDS

• Biomarkers • Infection • Infants • Late-onset

Early and accurate diagnosis of late-onset neonatal sepsis (LONS) is a major diagnostic challenge in neonatology.[1,2] LONS occurs most frequently in preterm and very low-birth-weight (VLBW) infants and in newborns with surgical conditions that require prolonged parenteral nutrition and hospitalization in the neonatal intensive care unit (NICU). A recent multicenter survey suggests that more than one-fifth (21%) of VLBW infants have at least 1 episode of late-onset culture-proven sepsis.[2] To date, clinical differentiation between LONS, including septicemia, meningitis, and systemic infection/inflammation (eg, necrotizing enterocolitis [NEC]), and noninfectious conditions (eg, acute exacerbation of bronchopulmonary dysplasia, apnea of prematurity, and gastrointestinal dysmotility) remains difficult, if not impossible, at an early stage of the illness.[1,3] A test or biomarker, which can accurately identify active infection/inflammation including septicemia and NEC in these vulnerable patients, would provide invaluable information for diagnosis and management. This review focuses on (1) the properties of an ''ideal'' diagnostic marker (or panel of biomarkers) of infection, (2) different categories of inflammatory mediators, such as acute phase proteins, chemokines, cytokines, and cell-surface antigens, that could potentially be used as clinical biomarkers, and (3) the use of molecular and biogenetic techniques for identification of pathogens in sterile body fluids. The authors also discuss recent scientific advances to search for novel biomarkers of infection in newborns.

THE IDEAL BIOMARKER OR TEST FOR LONS

The authors have previously proposed a set of clinical and laboratory criteria to assist neonatologists in identifying the ideal diagnostic marker of infection.[1] Although the

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Department of Pediatrics, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong
* Corresponding author. Department of Pediatrics, Level 6, Clinical Sciences Building, Prince of Wales Hospital, 30-32 Ngan Shing Street, Shatin, New Territories, Hong Kong.
E-mail address: pakcheungng@cuhk.edu.hk

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fundamental principles remain unchanged, with continuing advances in technology, neonatologists now expect more clinical information to be provided by biomarkers. **Box 1** summarizes current views on the characteristics of the ideal biomarker. The biomarker should not only serve as a guide on when to stop antimicrobial treatment in noninfected infants but also aid in the decision of whether to start antibiotic treatment at the onset of nonspecific clinical signs. With advances in molecular biogenetic techniques, the ideal biomarker or test is also expected to pinpoint precisely the identity or category of microorganism causing sepsis.[4] Information on the severity of infection and likelihood of progression to disseminated intravascular coagulation (DIC) would also provide invaluable insights to clinicians for targeting infants with sepsis who are most in need of urgent treatment and intensive care support.[5] Identification of the pathogen and antibiotic susceptibility profile at disease onset would also contribute enormously to acute management.

Box 1
The ideal biomarker or test for LONS

Clinical properties

1. Provide an algorithm for starting and/or stopping antimicrobial treatment. Such biomarkers should have
   - A well-defined cutoff value
   - A sensitivity and negative predictive value approaching 100% for "ruling out" LONS (but simultaneously having high specificity and positive predictive value >85%)

Note: A biomarker or test with very high specificity and positive predictive value can be used for ruling in sepsis

2. Detect infection early (ie, at clinical presentation)
3. Identify a specific pathogen or a category of pathogens (eg, viral, bacterial, and fungal organisms; gram-positive organisms vs gram-negative organisms; a specific species of pathogen)
4. Monitor disease progress and guide antimicrobial treatment (eg, bacterial antibiotic resistance gene detection)
5. Predict the disease severity at the onset of infection (eg, identify the type of virulent pathogen, predict DIC at the onset of disease presentation)
6. Predict prognosis (ie, mortality)

Laboratory properties

1. Stable compound that may allow an adequate time window for specimen collection within normal working hours (ie, sustained increase or decrease in biomarker level for at least 24 hours) or easy storage of the specimen without significant decomposition of the active compound until laboratory processing
2. Quantitative determination of biomarker concentration
3. Automatic and easy method of measurement
4. Quick turnaround time (ie, specimen collection, transport, laboratory processing time, and reporting of results to clinicians within 6 hours)
5. Small volume of specimen (ie, <0.5 mL blood)
6. Daily or on-demand availability of testing in clinical laboratories
7. Low-cost test that can be used as a routine measurement