Editorial

Pediatric Sepsis Biomarkers

Peter Dahlem[1] Marijan Saraga[2] Walter L. Strohmaier[3]

[1] Department of Pediatrics, Medical Center Coburg, Academic Hospital of the University of Split, Coburg, Germany
[2] Department of Pediatrics, University Hospital in Split, Split, Croatia
[3] Department of Urology, Medical Center Coburg, Academic Hospital of the University of Split, Coburg, Germany

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First of all, we congratulate the contributors of this special edition on "Pediatric Sepsis Biomarkers" for their outstanding work. They have been successful in providing a comprehensive review about all aspects of this disease to the potential readers.

Pediatric sepsis is a life-threatening disease, and almost all affected patients are admitted to a Pediatric Intensive Care Unit (PICU). Balazs and colleagues, in their review, summarize all the important primary and advanced diagnostic and therapeutic measures. Appropriate "golden hour" management will save many lives. Therefore, teaching young doctors and students should include lessons of the clinically visible "red flags" of early and specific sepsis symptoms. Appropriately initiated diagnostic tests to detect the pathogenic organism should immediately be followed by invasive therapeutic measures, such as fluid management, stabilization of respiration, and sufficient venous access. The term, systemic inflammatory response syndrome (SIRS), describes the symptoms resulting from the complex interaction between the pathogens, immune system, and vital organs. Staging of sepsis and SIRS is thus important to recognize the most vulnerable child supporting its organ function to avoid decompensation with organ failure. Standardized diagnostic and therapeutic regimes and algorithms are of additional great importance for effective and rapid management. Finally, appropriate antibiotic regimes should cover the spectrum of bacteria most commonly found in cultures. For patients with intensive care, advanced pediatric life support with mechanical ventilation and catecholamines should be started as early as possible. Complications such as acute lung injury, disseminated intravascular coagulation, and circulatory failure require the attention of the pediatric intensivist based on the best available evidence.

Blatt et al point out that for the most vulnerable children, newborns, and premature infants, sepsis is a devastating diagnosis. The early clinical symptoms are difficult to detect, and parents and caregivers should be alerted when the infant changes behavior or shows altered vital signs. The general principles of early diagnosis and therapy should be applied similarly to the pediatric age group. In addition to these principles, Blatt et al summarize the distinctive features of the neonatal age group. The origin may be ascending bacterial infection after premature rupture of membranes with chorioamnionitis or the presence of Group B *Streptococcus* (GBS) in the vaginal flora during delivery. Furthermore, in neonates, early- and late-onset sepsis with distinctive features should be considered. Fortunately, with preventive strategies, the risk of GBS infection can be minimized by prophylactic antibiotic eradication. Most importantly, infants already admitted to a neonatal ward should be protected from nosocomial infections by hygiene standard operating procedures and education of caregivers and parents.

The reasons why an infant or child is hit by SIRS during a septicemia is more of a concern of genetic individuality. Elek et al collected in their review the most actual evidence of insights into relationships between genetic predisposition and sepsis-related molecular reactions. Basically, after contact with a bacterial germ, mediators of the immune-response system including the coagulation system are activated or downregulated by distinct genetic factors. In the future and by research progress in this field, our knowledge will significantly improve on estimating a child's susceptibility to severe SIRS. It is within the reach of realization that therapies will correct the individual genetic defects that are found to be responsible for cases of inappropriate activation of inflammatory responses after bacterial infection. Such control of overwhelming inflammatory reactions will prevent life-threatening collateral damage to all organs and improve outcome.

According to Markic et al, it is still not always possible to predict the presence of bacterial infection by clinical signs, even by laboratory tests. Despite this, we use the same

Address for correspondence Peter Dahlem, MD, PhD, Department of Pediatrics, Medical Center Coburg, Academic Hospital of the University of Split, Ketschendorferstr. 33, 96450 Coburg, Germany (e-mail: Peter.Dahlem@klinikum-coburg.de).

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laboratory tests for the detection of sepsis and differentiation of bacterial infections from viral, and sometimes fungal infections. These are C-reactive protein (CRP) and procalcitonin (PCT) tests. In their review, Markic et al noted low specificity (50%) of CRP in distinguishing bacterial from viral infections, especially when CRP was slightly increased. A comparison between CRP and PCT showed better performances (sensitivity and specificity) of PCT than CRP despite the presence of similar weaknesses. While future studies are awaited on more specific biomarkers, these tests are still widely used in the diagnosis of sepsis.

The pathogenesis of sepsis is strongly linked to the function of proinflammatory, anti-inflammatory, and multiple function cytokines. It means that an interplay of these groups of factors can modulate the immune response in sepsis together with age, gender, and some environmental factors. Since the cytokines are genetically determined, clinical reaction to infection in sepsis is individual, while significant interindividual differences regarding the spectrum of their expression are caused by large variations and diversity in their expression. Although cytokines can be good markers of sepsis and point to possible differences of clinical expression in sepsis, they are not routinely used in practice due to many practical and technical problems. The accurate quantification of the cytokine levels, their different functions in real time, and short half-lives make their use difficult; so, the measurement of cytokine levels and functions has been left to the scientific laboratories only.

Although mortality and persistent morbidity in newborn infants and children with sepsis are highly significant problems, Dahlem et al summarize follow-up studies analyzing short-and long-term physical, mental, and psychological sequelae. The impact of bacterial sepsis on the child and its family differs between various pediatric age groups ranging from preterm and term neonates to school-aged children, adolescents, and young adults. In particular, prematurely born infants can develop sequelae directly attributable to prematurity and its consequences, in addition to sepsis-related lifelong effects compared with older children. This review comprises data from relatively small number of follow-up studies demonstrating that there is considerable impact not only on the patients' lives but also on their families. The relationship between health-related quality of life, severity of sepsis, and resulting handicaps per se is described. In future, large centers should establish structural follow-up programs for clinical and research purposes to learn more about the needs of affected children and their families. Furthermore, the prognostic relevance of biomarkers on long-term outcomes warrants clinical evaluation.

Finally, we want to emphasize that clinical markers summarized in the article of Szima et al are still the mainstay of early and rapid diagnosis above all laboratory tests. The training of primary physicians in this field e.g., simulated training, is essential to improve short- and long- term outcomes. In addition, with the purpose to confirm this thesis, appropriate long-term, follow-up studies are urgently needed. Thus, these two aspects serve as the "take home" messages to the readers of this special edition that can be implied in their teaching, as well as clinical and scientific work.