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ORIGINAL ARTICLE

Prognostic markers among Egyptian children with sepsis in the Intensive Care Units, Cairo University Hospitals

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Abstract
Background: Early identification of septic patients at risk of mortality is important in their prognosis.
Objective: Identification of septic patients at risk of mortality in Pediatric Intensive Care Units (PICUs) at Cairo University Hospitals, through measuring the levels of certain immunological parameters.
Methods: A hospital-based prospective cohort study was conducted in two PICUs at Cairo University Hospitals; all patients with diagnosis of severe sepsis or septic shock on admission were included. A total of 57 patients were prospectively followed at the selected PICUs and their demographic and clinical data were recorded. Microbiological and immunological workup (at days 1 and 7) was conducted for all patients to detect the causative organism of sepsis and to measure the levels of immunoglobulins (IgG, IgM and IgA), complement factors (C3 and C4), mature lymphocyte subpopulations (CD3+) and natural killer (NK) cells (CD3-CD16+CD56+), respectively.
Results: Mortality rate was 24.6%; the most frequent causes of death were multi-organ dysfunction and refractory shock. PELOD and PRISM III scores were significantly higher among non-survivors. At day 1, non-survivors had significantly higher levels of IgG, C4 and NK cells than survivors. However, from day 1 to day 7, survivors had a progressive increase in most of the immunological parameters (IgG, IgM, C4and CD3+ T lymphocytes). Survival curve analysis revealed the significant predictive ability of NK cells to detect early mortality.

Abbreviations: AUC, area under curve; NK, natural killer; PELOD, pediatric logistic organ dysfunction; PICUs, Pediatric Intensive Care Units; PRISM, Pediatric Risk of Mortality; SBP, systolic blood pressure; SPSS, statistical package of social sciences; ROC, receiver operating characteristics.

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Conclusion: Monitoring the levels of cellular and humoral immunological parameters together with assessing PELOD and PRISM III scores can significantly affect prognosis and survival of septic children.

Introduction

Egypt has made substantial progress in improving child health. According to the reported estimates, child mortality declined from 86 to 21 deaths per 1000 live births between 1990 and 2012, which represents a 75.4% drop. However, challenges remain to maintain the gains made through continued programmatic commitments.[1] Therefore, continuous development of precise estimates of the number of deaths of under-five children by cause is crucial. Sepsis is one of the leading causes of death in infants and children worldwide accounting for about 10% of the under-five children mortality, together with pneumonia.[2–4] In developing countries, sepsis is responsible for about 60–80% of children mortality, with more than 6 million neonates and children affected annually. Developing countries with large populations of children like Egypt bear the major burden of paediatric sepsis where a combination of environmental and socioeconomic factors like contaminated water, indoor air pollution, crowding and insufficient immunisation and nutrition, allow pathogens to invade and multiply relatively unchecked in the body.[4–6] According to Cairo University Hospitals' records in 2014, sepsis accounted for about 43% of cases admitted to the PICUs.

Despite extensive research about sepsis its pathophysiology remains poorly understood and the available data are controversial.[7] Sepsis is a systemic inflammatory disorder that involves complex interactions between complement, coagulation and fibrinolysis systems, and also activated cell elements (macrophages/monocytes, neutrophils, endothelial cells, thrombocytes, lymphocytes) and potentially toxic mediators produced by them.[8] In the most severe cases of infection, sepsis is associated with the release of huge amounts of pro-inflammatory cytokines and inflammatory mediators, which lead to devastating effects such as organ dysfunction and even death.[9]

Despite that, the important role of NK cells during sepsis was identified; however, they can play a beneficial or harmful function in the deleterious inflammatory process, depending on the circumstances and the type of bacterial infection.[9] At least two subsets of circulating NK cells have been recognised, the CD3-CD56 dim, which induces enhanced cytotoxicity, and the CD3-CD56 bright subsets which produce greater amounts of cytokines[9] including TNF, IFN-γ and GM- CSF, which are key mediators required to regulate the anti-infectious process.[10]

Early prediction of mortality in septic patients, through assessment of quantitative changes in key humoral and cellular parameters is crucial in prognosis and therapy.[11,12] Evaluation of these parameters is easily available in the vast majority of hospitals with critical care units. However, to the researchers' best knowledge, no data have been reported to fill the gap of knowledge in Egypt regarding this issue. The current study was conducted to identify septic patients at risk of mortality in the PICUs at Cairo University Hospitals, through measuring the levels of immunoglobulins (IgG, IgA and IgM), complement factors (C3 and C4) and lymphocyte subpopulations (T, B and NK cells) and finally setting recommendations based on the study results to improve the septic under-five children's prognosis and survival.

Subjects and methods

Study design, period and setting

This is a hospital-based prospective cohort study conducted at two PICUs at Cairo University Hospitals for identification of patients at risk of mortality by measuring alterations of key humoral and cellular parameters. The included units were: the PICUs of the Japanese Children Hospital on the ground and 4th floors, which included 28 beds and 14 beds, respectively. These units receive about 1420 patients annually. The study took place over a 9-month period from March 2014 to December 2014.

Working definitions

'Sepsis' was defined as suspected infection in the presence of two or more systemic inflammatory response syndrome criteria.[13] 'Severe sepsis' was defined as sepsis plus sepsis-induced organ dysfunction or tissue hypo-perfusion.[14] Sepsis-induced hypotension was defined as systolic blood pressure (SBP) < 90 mmHg, mean arterial pressure < 70 mmHg or SBP decrease >40 mmHg or <2 SD below normal for age in the absence of other causes of hypotension. 'Septic shock' was defined as hypotension (SBP < 90 mmHg) despite adequate fluid resuscitation (>1500 mL) or the use of vasoactive agents.[14]

Study sample

All patients admitted to the PICUs at Cairo University Hospital with severe sepsis or septic shock, were targeted for inclusion. A total of 67 patients were enrolled for the study and were prospectively followed at the selected PICUs from admission till hospital discharge or death. Ten patients were lost to follow up either due to death before the 7th day or due to insufficient samples to complete the laboratory workup, and that made a total of 57 patients enrolled.