Circulating Chemokine Levels in Febrile Infants With Serious Bacterial Infections

Hsiu-Lin Chen,[1,2] Chih-Hsing Hung,[1,3] Hsing-I Tseng,[1] and Rei-Cheng Yang[1,3]
[1]Department of Pediatrics, Kaohsiung Medical University Hospital; and [2]Department of Respiratory Therapy and [3]Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan.

Early diagnosis of serious bacterial infections (SBI) in febrile young infants based on clinical symptoms and signs is difficult. This study aimed to evaluate the diagnostic values of circulating chemokines and C-reactive protein (CRP) levels in febrile young infants <3 months of age with suspected SBI. We enrolled 43 febrile young infants <3 months of age with clinically suspected SBI who were admitted to the neonatal intensive care unit or complete nursing unit of the pediatric department of Kaohsiung Medical University Hospital between December 2006 and July 2007. Blood was drawn from the patients at admission, and complete blood counts, plasma levels of CRP, granulocyte colony-stimulating factor (G-CSF), and chemokines, including interleukin-8 (IL-8), macrophage inflammatory protein-1α, macrophage inflammatory protein-1β, monokine induced by interferon-γ, and monocyte chemotactic protein-1 were measured. Patients' symptoms and signs, length of hospital stay, main diagnosis, and results of routine blood tests and microbiological culture results were recorded. Twenty-six infants (60.5%) were diagnosed with SBI, while 17 (39.5%) had no evidence of SBI based on the results of bacterial cultures. CRP, IL-8 and G-CSF levels were significantly higher in the infants with SBI than in those without SBI. Plasma levels of other chemokines were not significantly different between the groups. The area under the receiver-operating characteristic (ROC) curve for differentiating between the presence and absence of SBI was 0.79 for CRP level. Diagnostic accuracy was further improved by combining CRP and IL-8, when the area under the ROC curve increased to 0.91. CRP levels were superior to IL-8 and G-CSF levels for predicting SBI in febrile infants at initial survey. IL-8 levels could be used as an additional diagnostic tool in the initial evaluation of febrile young infants, allowing clinicians to treat these patients more appropriately.

Key Words: C-reactive protein, chemokines, febrile infants, granulocyte colony-stimulating factor, serious bacterial infection
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The evaluation and management of young infants with fever is a common problem and can present pediatricians with a diagnostic challenge. Infants with elevated temperatures are at increased risk of serious bacterial infections (SBI), including bacteremia, meningitis, urinary tract infections (UTIs), and pneumonia [1,2]. Thus, a complete history-taking and physical examination are required to evaluate young infants in clinical practice. However, even infants who appear well may still have SBI [2,3].

Cultures from sterile sites are used as the gold standard to diagnose occult SBI; however, these results may not be available in the short term, and efforts have been made to find a reliable marker for the early identification of SBI. The ideal screening test should be able to predict which young infants are at increased risk of SBI, enabling clinicians to determine the need

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Address correspondence and reprint requests to: Dr Rei-Cheng Yang, Department of Pediatrics, Kaohsiung Medical University Hospital, Kaohsiung Medical University, 100 Tzyou 1st Road, Kaohsiung 80702, Taiwan.
E-mail: ch840062@kmu.edu.tw

for further workup and possible antibiotic therapy. Several methods of evaluation and diagnostic strategies have recently been suggested, but the need for a screening test remains a source of considerable debate.

Granulocyte colony-stimulating factor (G-CSF) is a colony-stimulating factor that not only augments the number of granulocytes, but also activates their microbicidal activity and inhibits their apoptotic response. The potential of G-CSF to enhance the host's inflammatory response to infection has been extensively investigated [4]. Chemokines (chemoattractant cytokines) represent a superfamily of small secreted proteins that function as intercellular messengers controlling the migration and activation of leukocytes involved in inflammatory reactions and immunity. Chemokines and proinflammatory cytokines are essential for initiation of the inflammatory response and defense against microbial infection [5,6]. Cells in most inflamed or infected tissues can release a variety of chemokines, and tissues infected with different bacteria release chemokines that recruit immune cells to sites of inflammation. Hence, chemokines play important roles at various stages throughout the infectious process [6,7].

The aim of this study was to evaluate and compare the diagnostic values of circulating levels of G-CSF and various potential chemokines for the early diagnosis of SBI in young febrile infants <3 months of age.

Patients and Methods

Ethical approval

The study was approved by the Human Experiment and Ethics Committee of Kaohsiung Medical University Hospital and informed consent was obtained from the parents of all patients before enrolment.

Patients

Febrile young infants <3 months of age with clinically suspected SBI who were admitted to the neonatal intensive care unit or complete nursing unit of the pediatric department of Kaohsiung Medical University Hospital between December 2006 and July 2007 were enrolled. The infants were suspected of having SBI if they had at least one of the following signs or symptoms: tachypnea, dyspnea, tachycardia, bradycardia, reduced activity, lethargy, or decreased appetite. Diagnostic work-up, including bacterial cultures, was performed to identify or rule out bacterial infection. Antibiotic therapy was prescribed for all enrolled patients at admission. Blood was collected at admission for the measurement of complete blood counts, C-reactive protein (CRP), and plasma chemokine levels. All infants included in the study were admitted to our hospital from the community; nosocomially infected infants were excluded.

SBI was defined as bacterial pathogens isolated from the cerebrospinal fluid or blood, a UTI, or pneumonia. Pneumonia was diagnosed by the presence of related clinical symptoms, such as tachypnea or a productive cough, along with a positive finding on chest X-ray. A UTI was diagnosed as pyuria and two sets of urine cultures with a single pathogen growth of $>10^4$ colony forming units/mL from a bladder catheterization, or $>10^5$ colony forming units/mL collected from a sterile collection bag [8]. The absolute neutrophil counts (ANC) and immature neutrophils/total neutrophils (IT ratio) were calculated according to the white blood cell (WBC) differential counts. The medical records of all patients with positive cerebrospinal fluid, blood, or urine cultures were thoroughly reviewed.

Measurement of CRP and circulating chemokine levels in plasma

Blood samples were collected in EDTA tubes at admission, and centrifuged immediately. The plasma samples for CRP levels were analyzed using rate turbidimetry (SYNCHRON® System(s)), Beckman Coulter Ireland Inc., Galway, Ireland). Plasma was frozen at –80°C until analysis of chemokines. Human Chemokines 6plex FlowCytomix Multiplex assay (Bender MedSystems GmbH, Vienna, Austria) was used according to the manufacturer's instructions to measure circulating levels of G-CSF and chemokines, including interleukin-8 (IL-8), macrophage inflammatory protein-1α (MIP-1α), macrophage inflammatory protein-1β (MIP-1β), monokine induced by interferon-γ (MIG), and monocyte chemotactic protein-1 (MCP-1). This assay requires a 25-μL serum sample. The standard ranges for this assay were: G-CSF, 34.3–25,000 pg/mL; IL-8, 13.7–10,000 pg/mL; MCP-1, 41.2–30,000 pg/mL; MIG, 6.9–5,000 pg/mL; MIP-1α, 13.7–10,000 pg/mL; and MIP-1β, 4.1–3,000 pg/mL.

Statistical analysis

Data entry and statistical analysis were performed using SPSS version 11.5 (SPSS Inc., Chicago, IL, USA).

Both median and range were calculated for continuous data. Variables were tested for their association with the diagnosis using χ^2 tests for categorical data and Mann-Whitney U tests for numerical data. The diagnostic values of the different variables and the best cutoff values were determined using receiver-operating characteristic (ROC) curves. Sensitivity, specificity, and positive and negative predictive values were calculated for the cutoff points that represented the best discrimination, as derived from the areas under the ROC curves. Correlations between chemokine levels and biological features or clinical outcomes were assessed using Spearman's correlation tests. A two-tailed p value < 0.05 was considered statistically significant.

Results

Forty-three febrile infants < 3 months of age who were admitted to the pediatric department of Kaohsiung Medical University Hospital were enrolled in this study. A total of 26 infants (60.5%) were diagnosed with SBI, while 17 (39.5%) had no evidence of SBI, based on the results of bacterial cultures. The characteristics and clinical findings of these two groups are shown in Table 1. There were no differences in sex or age between the two groups. Significantly greater percentages of infants with SBI had respiratory distress symptoms (tachypnea, chest retraction, cyanosis, nasal flaring, or grunting) and gastrointestinal symptoms (decrease of appetite, vomiting, or diarrhea), compared with infants without SBI. There were no differences between the groups in terms of vital signs recorded at admission, including body temperature, pulse rate, and respiratory rate. The causes of SBI included two cases of pneumonia (one with positive urine group B streptococcal antigen test), three cases of sepsis (*Escherichia coli*, *Salmonella* spp. and oxacillin-resistant *Staphylococcus epidermidis*), and 21 cases of UTIs. *E. coli* was the most frequent causative organism of UTIs ($n = 15$, 71.4%). *Proteus mirabilis* ($n = 3$) and *Enterococcus faecalis* ($n = 3$) were also identified.

The laboratory tests at initial evaluation (Table 2) revealed no significant differences between the two groups in terms of total WBC counts, ANC, IT ratios, hemoglobin, or platelet counts. CRP, IL-8, and G-CSF levels, however, were significantly higher in infants with SBI. Levels of other plasma chemokines, such as MIP-1α, MIP-1β, MIG, and MCP-1 were comparable between the groups.

The sensitivity, specificity, positive predictive value, negative predictive value, and the best cutoff values of CRP, IL-8, and G-CSF based on ROC analysis are presented in Table 3. The diagnostic properties of CRP, IL-8, and G-CSF levels were compared by calculating the areas under the ROC curves. The areas under the ROC curves for differentiating between the presence and absence of SBI were 0.79 (95% CI, 0.65–0.92) for CRP levels, 0.71 (95% CI, 0.56–0.86) for IL-8 levels, and 0.68 (95% CI, 0.52–0.84) for G-CSF (Table 3). CRP with a cutoff value of 13.6 μg/mL had a better diagnostic accuracy than IL-8 or G-CSF levels for predicting febrile infants with SBI at initial survey. Diagnostic accuracy was further improved by combining CRP with either IL-8 or G-CSF, for which

Table 1. Clinical characteristics of febrile infants with and without serious bacterial infections (SBI) at admission*

	Infants with SBI ($n = 26$)	Infants without SBI ($n = 17$)	p
Age (d)	52 (1–90)	38 (4–90)	0.822
Sex (male:female)	20:6	11:6	0.383
Respiratory distress symptoms† (%)	26.9	0	0.019
Gastrointestinal symptoms and signs‡ (%)	53.8	23.5	0.049
Vital signs at admission			
Body temperature (°C)	37 (36.4–39.3)	37 (36.7–38.7)	0.410
Pulse rate (/min)	150 (126–181)	152 (130–195)	0.390
Respiratory rate (/min)	46 (26–136)	49 (30–58)	0.275
Length of hospital stay (d)	8 (5–30)	7 (2–10)	0.058

*Continuous data presented as median (range); †including tachypnea, chest retraction, or cyanosis; ‡including decrease of appetite, vomiting, or diarrhea.

Table 2. Laboratory variables of febrile infants with and without serious bacterial infections (SBI) at admission*

	Infants with SBI ($n=26$)	Infants without SBI ($n=17$)	p
Corrected WBC count (/mm^3)	11,785 (4,620–22,000)	11,450 (4,250–21,590)	0.364
Absolute neutrophil count (/mm^3)	5,216 (1,010–16,280)	3,925 (1,110–11,010)	0.190
IT ratio	0 (0–0.43)	0 (0–0.12)	0.867
Hemoglobin (g/dL)	11.2 (8.7–21.6)	11.9 (9.3–16.5)	0.804
Platelet count ($\times 10^3$/mm^3)	383 (190–895)	337 (205–683)	0.233
CRP (μg/mL)	14.7 (0–153.7)	1.7 (0–13.6)	0.002
Chemokines			
G-CSF (pg/mL)	15.6 (0–992.7)	0 (0–298.8)	0.032
IL-8 (pg/mL)	0 (0–4,745.7)	0 (0–0)	0.002
MIP-1α (pg/mL)	138.8 (0–7,307.9)	0 (0–974.8)	0.229
MIP-1β (pg/mL)	88.6 (0–2,343.8)	69.3 (0–189.6)	0.235
MCP-1 (pg/mL)	912.8 (0–10,310.4)	1,087.7 (0–9,595)	0.803
MIG (pg/mL)	242.6 (0–1,620.2)	253.1 (0–938.2)	0.566

*Continuous data presented as median (range). WBC = white blood cell; IT ratio = immature neutrophils/total neutrophils; CRP = C-reactive protein; G-CSF = granulocyte colony-stimulating factor; IL-8 = interleukin-8; MIP-1α = macrophage inflammatory protein-1α; MIP-1β = macrophage inflammatory protein-1β; MCP-1 = monocyte chemotactic protein-1; MIG = monokine induced by interferon-γ.

Table 3. Diagnostic accuracy of CRP, IL-8 and G-CSF levels in febrile infants with serious bacterial infections at admission*

Test result variables (best cutoff value)	Sensitivity (%)	Specificity (%)	Positive predictive value	Negative predictive value	Area under the ROC curve
CRP (≥ 13.6 μg/mL)	58 (43–73)	100	1.0	0.61 (0.46–0.75)	0.79 (0.65–0.92)
G-CSF (≥ 50.8 pg/mL)	46 (31–63)	88 (77–99)	0.86 (0.75–0.96)	0.52 (0.37–0.67)	0.68 (0.52–0.84)
IL-8 (≥ 59.7 pg/mL)	42 (28–57)	100	1.0	0.53 (0.38–0.68)	0.71 (0.56–0.86)
CRP ≥ 13.6 μg/mL and/or G-CSF ≥ 50.8 pg/mL	73 (60–86)	88 (77–99)	0.90 (0.82–0.99)	0.68 (0.54–0.82)	0.81 (0.67–0.94)
CRP ≥ 13.6 μg/mL and/or IL-8 ≥ 59.7 pg/mL	77 (64–90)	100	1.0	0.74 (0.61–0.87)	0.91 (0.78–0.99)

*95% confidence intervals presented in the parentheses. CRP = C-reactive protein; IL-8 = interleukin-8; G-CSF = granulocyte colony-stimulating factor; ROC = receiver-operating characteristic.

the areas under ROC curves were increased to 0.91 and 0.81, respectively (Table 3; Figure).

There was positive correlation between IL-8 levels and the length of hospital stay (Spearman's correlation coefficient = 0.419, $p = 0.005$). No correlation was found between levels of CRP or other chemokines and clinical outcome. There were no correlations between chemokine levels, CRP levels, total WBC count, ANC, IT ratio, and microbial species.

Discussion

In this study, we simultaneously evaluated levels of CRP, G-CSF and several chemokines (MIP-1α, IL-8, MIP-1β, MIG, and MCP-1), and demonstrated that CRP had the best specificity and sensitivity for predicting SBI in febrile infants < 3 months of age. However, the combinations of CRP with IL-8 or G-CSF were superior to CRP alone for the early prediction of

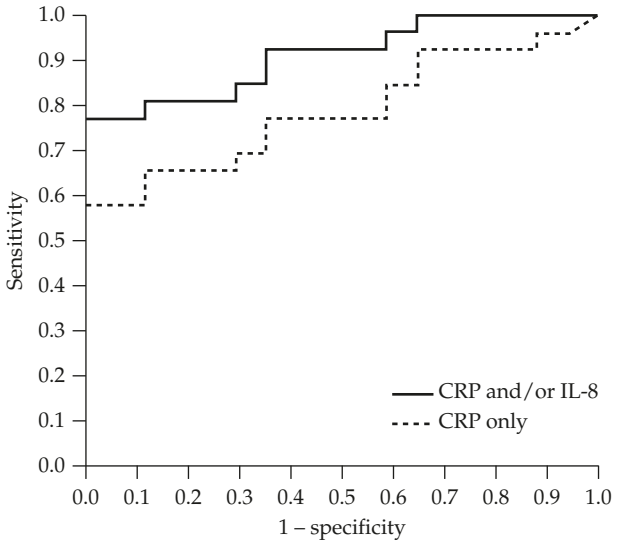

Figure. *Receiver-operating characteristic curves for various cut-off values of C-reactive protein (CRP) and interleukin-8 (IL-8) for detecting serious bacterial infections in febrile infants.*

SBI in these infants. MIP-1α, MIP-1β, MIG, and MCP-1 levels, however, could not be used to differentiate between SBI and non-SBI diseases in febrile young infants.

Early identification and management of SBI in febrile young infants is needed due to the less effective defense system of young infants and the high morbidity associated with SBI [2]. Unfortunately, however, there are currently no reportedly reliable clinical symptoms, signs, or laboratory tests suitable for the early diagnosis of SBI in these patients. Bacterial cultures provide the gold standard procedure for detecting occult SBI, but the results of this procedure are not promptly available. Efforts to find a reliable marker for the early identification of SBI are therefore ongoing.

Total WBC count, ANC, and immature neutrophil levels are the common tests used for screening SBI in clinical settings. These tests, however, are not always able to distinguish between bacterial infections and respiratory viral infections in young febrile children [9–12], as shown in the current study. CRP has recently become the most commonly used marker for both the early recognition of clinically undetectable SBI and an indicator of the need for further management. CRP concentration has been reported to be both more sensitive and more specific than either total WBC count or ANC [13–15]. Although CRP demonstrated good diagnostic accuracy in this study, previous reports have found CRP to be an unsatisfactory marker for identifying young infants with SBI [16–18]. A single CRP measurement cannot be used to definitively diagnose SBI [18].

Chemokines have recently become a focus of interest for inflammation and infection research. Chemokines play a major role in diseases with an accentuated inflammatory component, and have been found at similar levels in the serum of neonates and adults [19–22]. Among the various chemokines, IL-8 is produced predominantly by monocytes, macrophages, and endothelial cells in response to various stimuli, such as lipopolysaccharide and tumor necrosis factor-α [23]. This chemokine is one of the major mediators of the inflammatory response. IL-8 plays an important role in the release, activation, and chemotaxis of neutrophils. Several studies have shown that serum IL-8 levels are increased in newborns with culture-proven sepsis [24–29]. Kurt et al and Kocabas et al also reported that plasma IL-8 levels were higher in septic than in non-septic newborn infants [24,26]. We also found a positive correlation between IL-8 levels and the length of hospital stay. This suggests that IL-8 could serve as a predictor of disease outcome, but not as a good indicator of SBI. However, we found that levels of IL-8 and G-CSF, a factor influencing neutrophil function, were significantly increased in the SBI group and showed high specificity for differentiating bacterial infection in febrile infants.

CRP, IL-8, and G-CSF alone demonstrated moderate accuracies (areas under the ROC curves 0.7–0.9) for diagnosing SBI in febrile infants. However, the accuracy was improved (area under the ROC curve >0.9) by combining IL-8 and CRP values. This result implies that CRP and IL-8 levels could serve as indicators for the early prescription of antibiotics.

In conclusion, these results demonstrate that CRP levels are superior to IL-8 and G-CSF levels for predicting SBI in febrile infants at initial survey. The combination of the inflammatory marker IL-8 with CRP could improve the sensitivity and specificity of SBI detection in febrile young infants, thus allowing clinicians to treat these patients more appropriately.

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嚴重細菌感染之發燒嬰兒的細胞趨化激素濃度表現

陳秀玲[1,2] 洪志興[1,3] 曾馨誼[1] 楊瑞成[1,3]

[1]高雄醫學大學附設醫院 小兒科部

高雄醫學大學醫學院 [2]呼吸治療學系 [3]醫學系

在小於 3 個月以下的發燒小嬰兒，以病人臨床表現及現有之實驗室檢查都不足以完全預測有無嚴重細菌感染 (serious bacterial infection, SBI) 。本研究的目的是評估血中的顆粒球生長激素 (GCSF)、細胞趨化激素 (chemokines) 及 C 反應蛋白 (CRP)，在小於 3 個月大之發燒嬰兒鑑別嚴重細菌感染之診斷能力。研究對象為年齡小於 3 個月的發燒嬰兒，因臨床上懷疑有嚴重細菌感染，在 2006 年 12 月至 2007 年 7 月間，住入高雄醫學大學附設醫院小兒科新生兒加護病房或中重度病房的病人。在入院時抽血測一般血液檢查、CRP、G-CSF 及細胞趨化激素濃度，並作血液、尿液或腦脊髓液細菌培養。細胞趨化激素的測定內容包括 interleukin-8 (IL-8) ，macrophage inflammatory protein-1 α ，macrophage inflammatory protein-1 β ，monokine induced by interferon-γ ，and monocyte chemotactic protein-1。病人依細菌培養之結果將病人分成 SBI 及 non-SBI 兩組來比較各類變項。結果共有 43 位小於 3 個月的發燒嬰兒納入本研究，SBI 組共有 26 位 (60.5%)，而 non-SBI 組共有 17 位 (39.5%)。統計分析顯示 CRP、GCSF 及 IL-8 在 SBI 組比起 non-SBI 組有顯著的上升。而其他細胞趨化激素則在兩組中無顯著差異。以 CRP 的診斷能力而言，其 receiver-operating characteristic (ROC) 曲線下面積可達 0.79。若將 CRP 與 IL-8 合併來看，則更可提高對於 SBI 的診斷率，在 ROC 曲線下面積可增至 0.91。我們的結論是 CRP 在早期鑑別小於 3 個月的發燒嬰兒有無細菌性感染，優於 IL-8 與 GCSF。但在初步評估發燒嬰兒上，IL-8 可作為 CRP 以外的輔助診斷工具，以使臨床醫師在處置發燒嬰兒時可提早及時使用抗生素。

關鍵詞：C 反應蛋白，細胞趨化激素，發燒嬰兒，顆粒球生長激素，嚴重細菌感染

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通訊作者：楊瑞成醫師

高雄醫學大學附設醫院小兒科部

高雄市 807 自由一路 100 號