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Usefulness of the Acute Phase Reactants (APR) Score [Part 4]: Transient Elevation of Acute Phase Reactants in the Early Neonatal Period is Due to Inflammation Not Infection

Toshihiko Nakamura[1]*, Haruo Goto[2], Jin Xiuri[3] and Shingo Yamada[3]

[1]*Department of Neonatology, Japanese Red Cross Musashino Hospital, Japan*

[2]*Department of Pediatrics, Nagoya City University West Medical Center, Japan*

[3]*Immunology and MDx Unit, Shino-Test Corporation, Japan*

***Corresponding author:** Toshihiko Nakamura, Department of Neonatology, Japanese Red Cross Musashino Hospital, 1-26-1 Kyonan-cho, Musashino city, Tokyo 180-8610, Japan

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ABSTRACT

Purpose: To investigate whether transient elevation of acute phase reactants (APRs) in the early neonatal period reflects infectious disease.

Subjects and Methods: The subjects were 157 infants who were admitted to a single-center NICU in a one-year period and in whom the acute phase reactant score and white blood cell count was determined by blood sampling on at least 3 consecutive days from early after birth. Inflammatory disease groups that may increase APRs were classified into the fetal inflammatory response syndrome (FIRS) group, the fetal/neonatal asphyxia group, and the noninflammatory group. Differences in daily changes and significant differences in peak values were examined for each substance in the presence or absence of antibiotic therapy.

Results: WBC and CRP peaked at 1 day of age and declined in all groups. No significant difference was observed in the peak values. There was no significant difference in AGP or Hp at 3 days of age. All groups were examined with or without antibiotic therapy and similar results were obtained.

Conclusion: The early postnatal elevation of APRs occurred as a result of perinatal stress-induced inflammatory changes rather than bacterial infection.

Keywords: APR Score; Antibiotic Therapy; Early Neonatal Period; Fetal Inflammatory Response Syndrome; Transient Increase in APRS

Introduction

The transient CRP elevation in the early postnatal period has been described as physiological, perinatal stress, and even bacterial infection that cannot be detected by simple recent cultures [1-5]. Differences in changes in CRP between infants born by planned cesarean section and infants born by emergency cesarean section, meconium aspiration, or forceps delivery have also been evaluated, and it has been reported that the transient increase in CRP is the result of some perinatal stress. In clinical practice, it cannot be denied that delays in the treatment of infections, especially those that occur immediately before or after birth, can lead to a fatal outcome for the infant, and as a result, antibiotic prophylaxis cannot be ruled out in many cases. We evaluated the utility value of the APR score and examined changes in the APR score, including CRP, in the early postnatal period, in infants with no obvious intrauterine infection.

Subjects and Methods

From January 1, 2010, to December 31, 2010, a total of 440 infants were admitted to the neonatal intensive care unit of National Organization Hospital, Nishi-Saitama Chuo National Hospital, Perinatal and Maternal and Fetal Medical Center; 195 infants were hospitalized within 24 hours after birth. Among these, 159 infants in whom the APR score was measured on ≥3 consecutive days were included in the study. A total of 159 patients had a condition associated with a possible increase in APR score, including fetal inflammatory response syndrome (FIRS) and fetal/neonatal asphyxia (including meconium aspiration syndrome). However, cases in which these conditions could not be distinguished from infectious pneumonia were excluded. The patients were classified into 3 groups: 2 inflammatory groups and 1 noninflammatory group. The noninflammatory group included uncomplicated preterm infants, low birth weight infants, and infants with respiratory distress who could be managed with oxygen administration in an incubator with FiO2 ≤ 0.3 or nasal CPAP alone.

The 3 groups were each further classified into 2 groups based on the presence or absence of antibiotic therapy. Indications for the administration of antibiotics include signs of intrauterine infection in the mother and fetus (foul odor of amniotic fluid and vaginal secretions flowing out due to premature rupture of membranes, persistent fever of ≥38°C, maternal tachycardia, fetal tachycardia, uterine tenderness, etc.), and the presence of respiratory distress in preterm infants. In the case of obvious signs of infection ("not doing well"), the infants were judged to have clinical sepsis and were excluded from this study. Four APR items (C-reactive protein; CRP, α1-acid glycoprotein; AGP, and haptoglobin; Hp) and the peripheral blood leukocyte count were examined over time. In each of the 3 groups, the transition of patients managed with and without antibiotic therapy and the presence or absence of a significant difference in the maximum value were examined.

The APR was measured using a Shinotest QuickTurbo C™ (SHINOTEST Co. Sagamihara, Japan). The limits of detection of the Shinotest Quick Turbo C™ were as follows: CRP <0.25 mg/dL, AGP <20 mg/dL, and Hp <20 mg/dL. For the sake of convenience, in the case of values below these limits of detection, "0 mg/dL" was applied to the measured value. Organization Nishisaitama Chuo National Hospital, and written informed consent was obtained from the parents or guardian of the hospitalized newborns. Statistical analysis was performed using Stat Mate VTM (ATMS Co. Tokyo, Japan) statistical software. The student's t-test was applied when the groups divided by the presence or absence of antibiotic therapy in each group had the homogeneity of variance, and Welch's test was applied when they did not have the homogeneity of variance. The one-way analysis of variance was performed to evaluate the change over time in each group. In addition, the $\chi 2$ test was used for the difference in the ratio of diseased groups in each group divided by the presence or absence of antibiotic administration. In both cases, $p<0.05$ was judged to be a significant difference.

Results

The number of cases and patient background factors according to the presence or absence of antibiotic therapy in the 3 groups (Table 1): In the noninflammatory group, the number of infants who received antibiotic therapy was clearly small, and in patients with inflammatory response syndrome (FIRS) derived from intrauterine infection, the number of infants who received antibiotics was significantly higher ($p<0.001$). When the three groups were combined, there was no significant difference in gestational age or birth weight between patients managed with or without antibiotic therapy. Only two infants were diagnosed with an intrauterine infection during the study period. The average duration of antibiotic therapy in the 58 cases (after excluding the 2 cases of infection) in the antibiotic group was 3.26 days (range: 2-6 days). Trends in APRs and white blood cell count (WBC) in each group (Figures 1A-1D): In the inflammatory disease group, fetal asphyxia group, and FIRS group, the changes in APRs were ascertained when CRP peaked 1 day after birth. After determining the value, a peak-out trend was commonly observed. AGP and Hp peaked 2-3 days after CRP and then declined. When the peak CRP values were compared between patients managed with and without antibiotic therapy, no significant difference was observed in any of the three groups. The peak values of AGP and Hp did not differ between the patients managed with and without antibiotic therapy. The WBC count showed almost the same transition as the CRP value.

Table 1: Comparison of patient background with and without antibiotic therapy.

	antibiotics (+)	antibiotics (-)	p
Non-inflammation group	29	84	
Inflammation group			
• Fetal/Neonatal asphyxia	11	10	
• FIRS	18	5	
Total	58	99	p<0.001
Gestational Age (weeks)	36.0±4.4	36.1±2.5	NS
Birth Weight (grams)	2260±99	2280±70	NS
Male/Female	37/19	54/45	NS
Duration of antibiotic administration (days) mean(range)	3.26 (2-6)	-	

FIRS; fetal inflammatory response syndrome, NS; not significant

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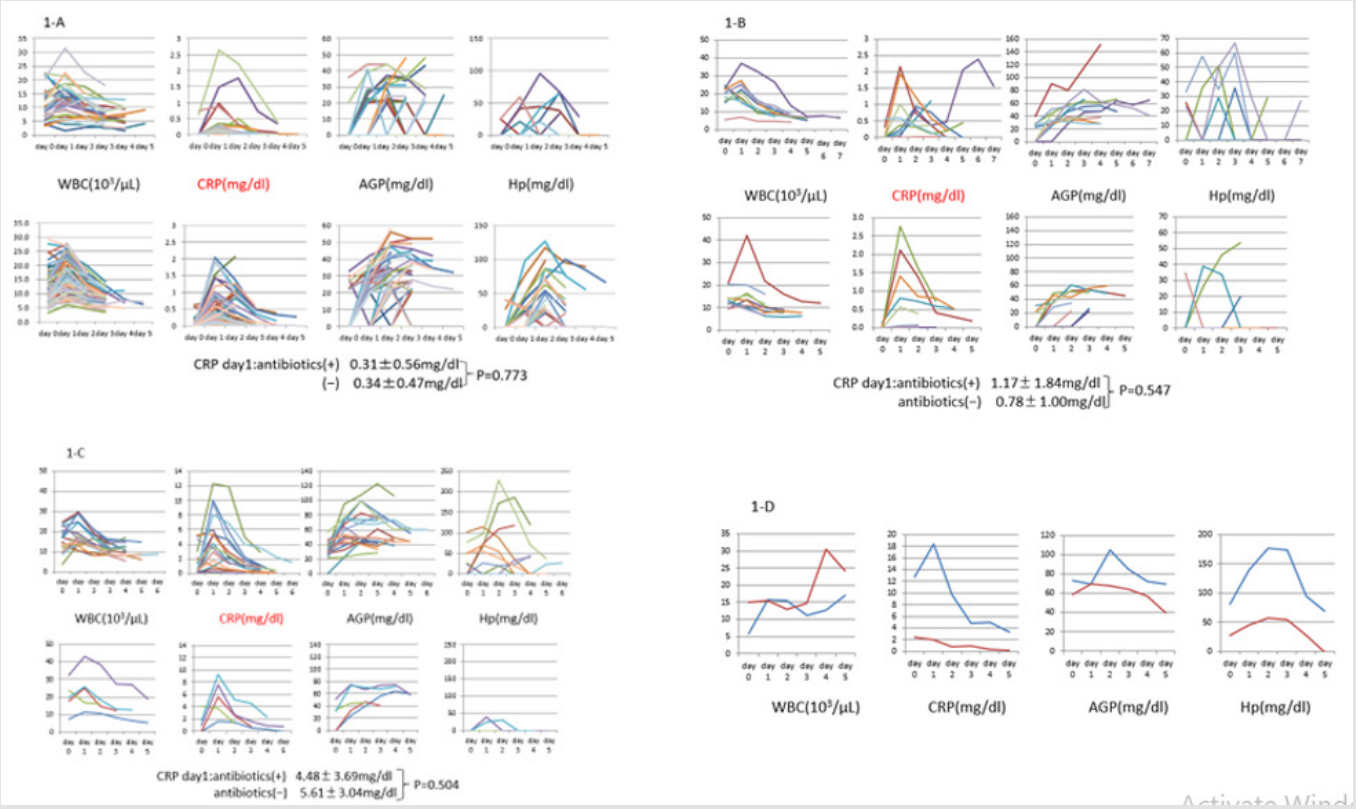
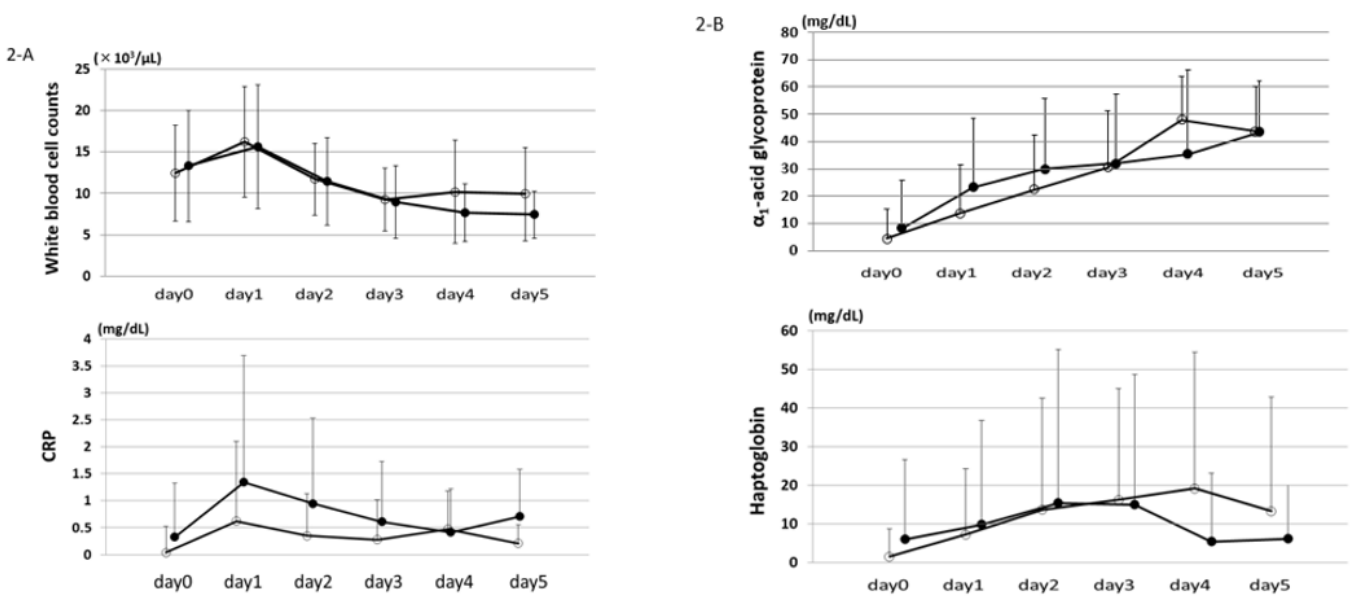


Figure 1: Serial changes of white blood cell count and APRs in each disease group.
A. Non-inflammation group.
B. Fetal and neonatal asphyxia group belonging to the inflammation group.
C. Fetal inflammatory response syndrome group belonging to inflammation group.
D. Infection group.
The upper row shows the group with antibiotic therapy, and the lower row shows the group without antibiotic therapy. No significant difference was observed between the upper and lower rows.

Comparison of changes in WBC and APR with and without administration of antibiotics (Figures 2A & 2B): The infectious disease group was excluded because the use of antibiotics was essential. The remaining 3 groups were combined, and changes in WBC and APRs with and without the use of antibiotics were examined. WBC and CRP peaked at 1 day of age. Significant differences in the WBC count (15.9±7.4×103/μL vs. 16.3±6.7×103/μL [p=0.178]) and in the CRP values (1.34±5.64mg/dL vs. 0.65±1.99 mg/dL [p=0.052]) and neither was accepted. Since AGP and Hp decreased sharply at 4 and 5 days of age in samples without antibiotic therapy, these values were compared at 3 days of age. The AGP values of the groups managed with and without antibiotics were 36.3±25.9 mg/dL and 30.4±20.7 mg/dL, respectively, (p=0.243), while the Hp values were 16.9±32.7 mg/dL and 16.2±28.7 mg/dL (p=0.913). These differences were not statistically significant.



Note: No significant difference was observed in all four biomarkers.

- The solid black circles indicate the group with antibiotic therapy, and the white circles indicate the group without antibiotic therapy.
- The value of each circle indicates the average value, the upward bar represents +SD, and downward bar represents -SD.

Figure 2: Serial changes of white blood cell count and APRs in each group with and without antibiotic therapy.

Discussion

If the timing of treatment for neonatal infection, especially early-onset sepsis, is missed, the prognosis of the infant will immediately deteriorate; thus, prevention, an early diagnosis, and early treatment are the principles of management [6-8]. Infections in newborns, especially premature infants, cause rapid deterioration of the general condition, and antibiotic prophylaxis is often unavoidable. The careless administration of antibiotics is believed to encourage the development of resistant bacteria [9]. Unnecessarily imposing the long-term administration of antibiotics while waiting for bacterial culture results is also a concern [10,11]. CRP is useful for diagnosing infectious diseases, but in contrast to cytokines and procalcitonin, there is a time lag of approximately 12 hours from the onset of infection until it increases in the blood. However, it is undeniable that cytokines decline early and that procalcitonin is problematic in terms of the cost associated with observing daily changes. Furthermore, it is considered that CRP increases once after birth, peaks at 48 hours after birth, and then declines. It has been reported that this peak value varies depending on the magnitude of the stress of birth [12]. It is logical that the production of cytokines stimulates the hepatic production of CRP induced by the stress of labor (i.e., the degree of hypoxic-ischemic injury), to lead to this phenomenon.

In addition, CRP elevation has been reported to occur as a response to some kind of infection. In Japan, Hayashida et al. found that the peak CRP values differed depending on whether patients received antibiotics. Since patients who received antibiotic therapy had significantly lower CRP values than those who did not, it was suggested that some types of bacterial infection could not be detected by culture, and the existence of a group that did not have a physiological increase in CRP was reported [5]. We investigated whether the transition of CRP differed depending on the presence or absence of antibiotics. In addition, the changes in the WBC count and three APRs related to the APR score (CRP, AGP and Hp) were examined simultaneously. The values of these four markers did not differ according to the presence or absence of antibiotic therapy. Therefore, it was concluded that these patients were not infected with any pathogenic organisms that could not be identified on bacterial culture examinations. We focused on the changes in the WBC count and CRP immediately after birth as a method of differentiating between early neonatal infection and inflammatory reaction in patients with elevated APR scores, including CRP. If the peak WBC count and CRP value are observed within 48 hours after birth, as in the results of this study, the possibility of infection is extremely low. Taking advantage of this fact, if the possibility of early neonatal sepsis cannot be denied at birth, broad-spectrum antibiotics (we mainly use ampicillin sodium and gentamicin, and we would like

to adopt ampicillin sodium with cefotaxime as appropriate) should be immediately administered. When WBC and CRP had peaked by 48 hours after birth, and the general condition of the infant was good and blood cultures were confirmed to be negative at 48 hours after birth, antibiotic therapy was aggressively terminated. Among these cases, no patients showed re-elevation of their WBC count or APR score.

Conclusion

The transient increase in CRP in early neonates in the absence of obvious infection is an inflammatory response to perinatal stress and is unaffected by the presence or absence of antibiotic therapy.

Disclosure

The authors declare no conflict of interest.

Author Contributions

The manuscript was written by TN. HG, JX and SY provided advice on the validity of the content of the paper. TN collected and analyzed data. All authors read and approved the final manuscript.

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