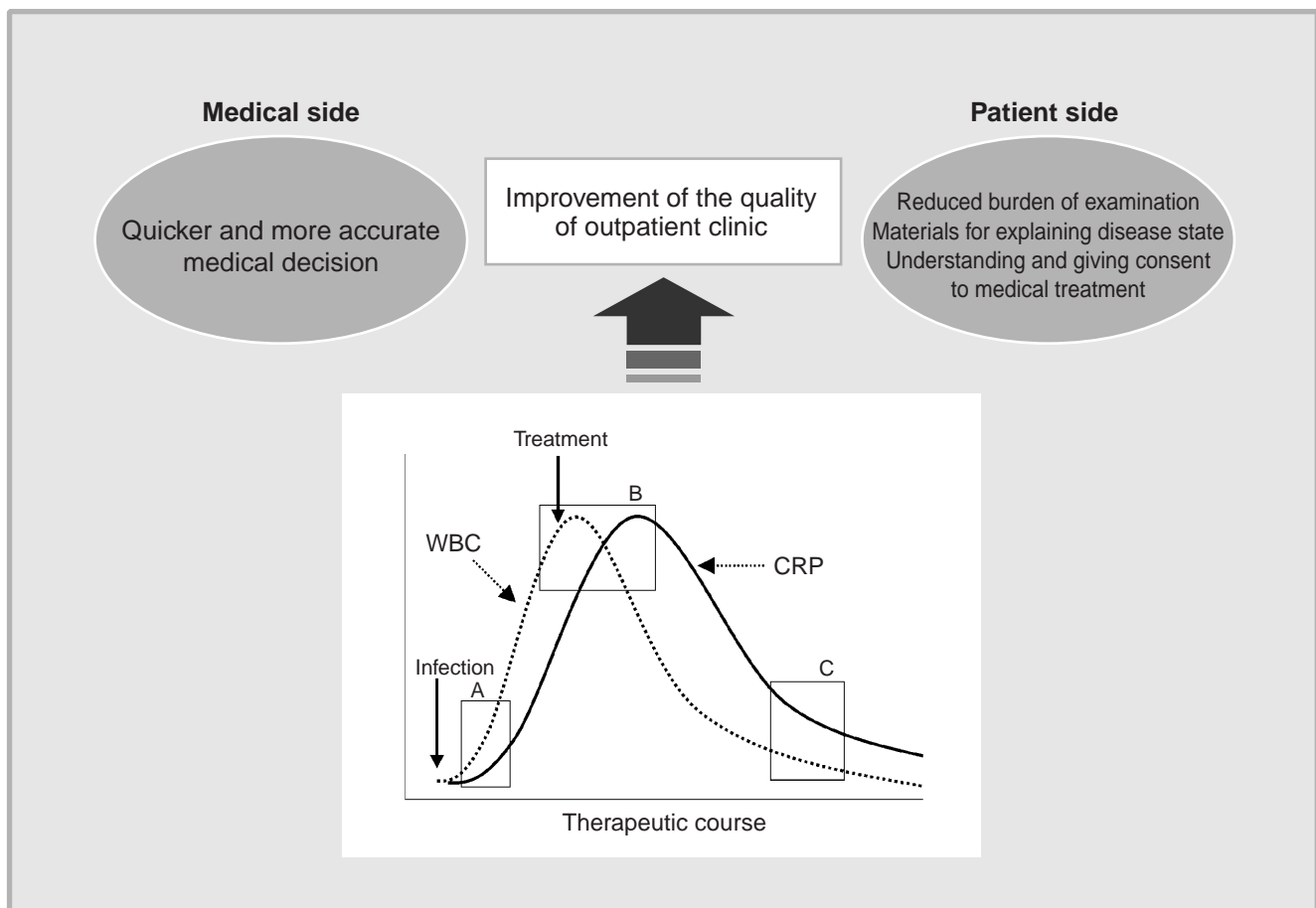


GUEST FORUM

Efficacy and Significance of Rapid Simultaneous CRP and WBC Testing in Pediatric Diagnostic Practice

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From time to time, the C-reactive protein (CRP) test and the white blood count (WBC) test are used by pediatricians to assist in diagnosing infectious disease, and to confirm the effect of treatment. When performing these tests, it is desirable to collect the smallest amount of blood possible; this is especially important when the patient is an infant.

This paper reports on a study of the Horiba LC-270 CRP Automatic Blood Cell Counter and CRP-Measuring Instrument in a pediatric outpatient clinic. The research examined the effect of performing simultaneous CRP and WBC tests using extremely small samples of blood. The authors collected data from 1,058 infants and conducted in-depth research on their conditions over the course of a one-year period beginning in November 1997. The results confirmed that the instrument was very useful in aiding diagnosis and treatment decisions, supporting informed consent, achieving medical economy, and delivering other benefits.

1

Introduction

Taking appropriate actions to treat infectious diseases is important in pediatric outpatient clinics. We are routinely faced with many difficulties in treating infectious diseases. For example, it is difficult to decide whether or not a patient should be hospitalized, whether or not infusion should be performed, or how we should treat an infant in apparent serious distress.

C-reactive protein (CRP) assay and white blood cell (WBC) count are useful for clinicians called upon to diagnose infectious diseases, determine their severity, and gauge the effects of therapy. Although these tests are frequently used as effective indicators, their clinical use has been limited because collecting blood samples from infants is often difficult, and because results from the blood tests cannot be obtained quickly.

The LC-270 CRP automatic blood cell counter and CRP-measuring instrument eliminates these limitations and allows clinicians to use the two parameters in clinical settings because the instrument can quickly perform measurements on very small volume blood samples. Particularly, the instrument is useful for supporting diagnostic decisions in difficult cases previously treated based on experiences and instincts. Because the results of these tests support a more accurate understanding of the state of a patient's health, they can help determine the therapeutic approach and can be used when explaining disease and treatment to patients' families. We expect that the introduction of this instrument will further improve the quality of care in outpatient pediatric clinics.

2

Methods

Our study sample consisted of 1,638 22-day-old to 13-year-old children who arrived at our hospital from November 1997 to November 1998. Of this total population, 1,058 patients were evaluated for quantitative determination of CRP and complete blood count (CBC) using the LC-270 CRP. The other 580 patients were evaluated for qualitative examination of CRP using the conventional latex agglutination method. All patients had the tests performed at the outpatient clinic. The effects of the examinations were reviewed for the following points:

- 1) A simple and painless technique for collecting an extremely small amount of blood was developed. Using this technique, a method for measuring CRP and CBC in a simple, quick, and painless manner was studied. For the qualitative examination of CRP we collected blood using Torstic™ brand disposable blood sugar self-measuring blood collectors imported by Hormet and distributed by Nippon Hoechst Marion Roussel. For the quantitative determination

of CRP and CBC, we collected blood using Microlet™ brand caps for deep centesis imported by Bayer Medical and distributed by Ono Pharmaceutical.

Centesis was made mainly at the head of the thumb or hypothenar eminence (Fig.1). The cap of the Microlet™ was replaced for sterilization every time it was used.



Fig.1. Blood collection from infant's patient.

- 2) The severity of the pain associated with blood collection was classified, based on the behavior and attitude of the patients, using a scale. The frequency for each grade on the scale was calculated.
- 3) The clinical effect on diseases, especially on infantile febrile diseases, was examined. Table 1 shows the main diagnostic results for the subjects as of August 1998.

Disease	Number of cases	Disease	Number of cases
Pharyngitis	139	Urinary tract infection	4
Bronchitis	294	Bacterial enteritis	7
Pneumonia	59	Bacterial meningitis	1
Influenza	33	MCLS	4
Influenza and bronchitis	70	Pertussis-like disease	3
Influenza and pneumonia	7	Febrile convulsion	10
Tonsillitis	40	Nasal bleeding	2
Exanthema subitum	16	Fever of unknown origin	4

Table 1. Diagnostic results from examined patients.

- 4) We analyzed the relationship of infectious disease to changes in CRP and WBC to determine the significance of using these two parameters in understanding the course and state of disease.
- 5) The effects of the qualitative and quantitative examinations of CRP at outpatient clinics were compared. The potential economic effect of the introduction of the instrument was examined.

3

Results

- 1) In more than 99% of the patients, the percutaneous technique for collecting an extremely small amount of blood to be used in the quantitative determination of CRP and CBC, or the qualitative examination of CRP could be immediately and easily used.
- 2) Patients' reactions to the pain associated with blood collection was compared before and after centesis in 200 consecutive patients. The results showed that the pain was reduced to a degree that 74% of the patients (A+B) did not cry (Fig.2).

Before / After centesis

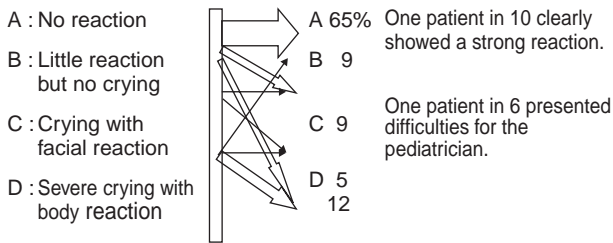


Fig.2. Classification of pain caused by blood collection.

- 3) The effects on LC-270 CRP measurements from the blood collection method (collection of extremely small amounts vs. conventional intravenous collection) were studied. The results are compared in Table 2.

	Correlation		Comparison of mean values		
	Correlation coefficient		Extremely small amount of blood collection	Intravenous blood collection	Significant difference
CRP(mg/dl)	r=0.997	p<0.01	1.99±1.46	1.99±1.47	N.S.
WBC(x10 ³)	r=0.988	p<0.01	11.4±4.8	10.4±4.3	p<0.01
RBC(x10 ⁴)	r=0.816	p<0.01	472±35	450±28	p<0.01
Hb (g/dl)	r=0.884	p<0.01	13.0±1.1	12.4±1.0	p<0.01
Ht (%)	r=0.886	p<0.01	39.1±3.5	37.0±3.1	p<0.01
Plt (x10 ⁴)	r=0.494	p<0.05	10.4±7.1	22.5±7.7	p<0.01
n=20					

Table 2. Correlation and statistical value of infinitesimal and venous blood collection.

When the technique for collecting an extremely small amount of blood is used, it is difficult to prepare commercial products of ethylenediaminetetraacetic acid salt (EDTA)-coated capillary tubes as specified by the manufacturer. Therefore, it is often inevitable that heparin anticoagulant-coated capillary tubes are substituted, and this compromises the reliability of the platelet (PLT) count (by producing an artificially low result).

Although it was impossible to determine the direct, strict correlation between the normal values of blood cell count by percutaneous blood collection and blood cell count by intravenous blood collection, we determined that parameters other than PLT could be clinically used regardless of the blood-collecting tubes used.

- 4) The instrument was useful for the screening of serious bacterial infections in infants (bacterial meningitis, advanced pneumonia, and urinary tract infection) and the improvement of the diagnostic accuracy and differential diagnosis of acute febrile diseases, such as exanthema subitum and mucocutaneous lymph node syndrome (MCLS or Kawasaki disease). Fig.3 shows data from a patient with bacterial meningitis detected by a qualitative examination of CRP.

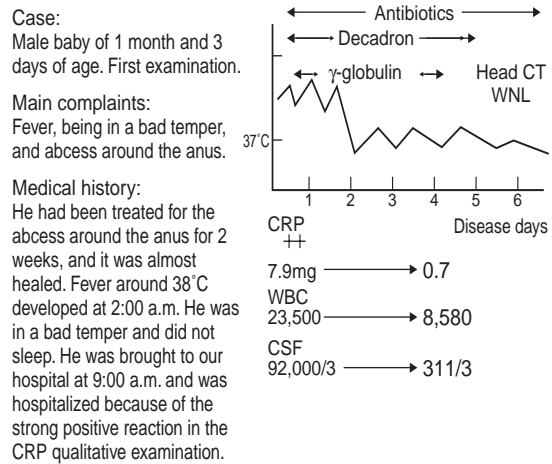


Fig.3. Progress of the symptoms of bacterial meningitis.

Table 3 presents data from six patients with urinary tract infection detected by the screening of CRP and WBC.

Case	Age	Sex	Duration of fever	CRP (mg)	WBC (x10 ³)	Hospitalization	Remarks
1	1m22d	F	<1 d	>10.0	22.5	+	Hydronephrosis
2	3m	M	<1 d	5.8	10.7	+	
3	3m	F	<1 d	+++5.8	22.8	+	
4	4m	M	<2 d	+++5.2	11.3	+	Atrophy of one kidney
5	5m	M	<2 d	+++16.0	18.1	+	
6	6y	F	<1 d	+++5.4	27.9	+	

Table 3. Screened 6 cases of a urinary tract infection.

Table 4 presents data from five patients with MCLS that were detected early through the examination of CRP and WBC.

Case	Age	Days of hospitalization	Symptom	CRP WBC	Main symptoms and frequency at examination
1	7m	4	1. 2. 3 Flare of the BCG site	2.7 10.2	1. Fever 5/5 2. Findings from the lips and oral cavity 4/5
2	7m	4	1. 2. 4 Flare of the BCG site	>10 18.5	3. Changes in the ends of the extremities 2/5 4. Injection of the conjunctiva of both eyes 2/5
3	1y6m	2	1. 2. 5	3.2 11.5	5. Non-purulent lymph node swelling 2/5 6. Atypical exanthema 1/5
4	2y11m	3	1. 5 Diagnosis when the case was referred to our hospital Cervical lymphadenitis	3.3 11.2	
5	5y1m	3	1. 2. 3 4. 6	5.1 10.8	

Table 4. Laboratory result abnormality and symptomatic frequency of Kawasaki Disease.

Based on the results from all of the patients examined, the fluctuations of CRP and WBC, categorized by disease, are summarized in Table 5. As shown in the figure, fluctuations of the two parameters were useful for differentiating diseases. Note that the figure indicates only the expected tendency of the fluctuations based on the clinical symptoms and experimental protocols used in this study. In practice, the fluctuations of the two parameters may be highly variable depending on the specific disease, its phase, duration of infection, and treatments.

WBC	CRP	Disease
↑	→	Early bacterial infectious disease, dehydration, leukemia, pertussis, and some viral and bacterial infections
↑	↑	Climax of bacterial infectious disease, Kawasaki disease (MCLS)
→	↗	Recovery stage of bacterial infectious disease, some viral and bacterial infections
↘	→	Viral infection

Table 5. Changes in WBC/CRP and disease.

5) Fig.4 illustrates a conceptual model of the fluctuation patterns of CRP and WBC in bacterial infection. At region A in the early stage of infection, WBC sharply increased, while CRP increased only slightly. At region B immediately before treatment was started, the two parameters reached their maxima. After treatment was started, WBC began to fall first. CRP increased for a short period (about 1 day) and then started to fall. At region C, in the recovery stage, WBC returned to normal, while CRP remained slightly elevated. A typical example of fluctuations in acute bacterial infection patients is shown in Fig.5.

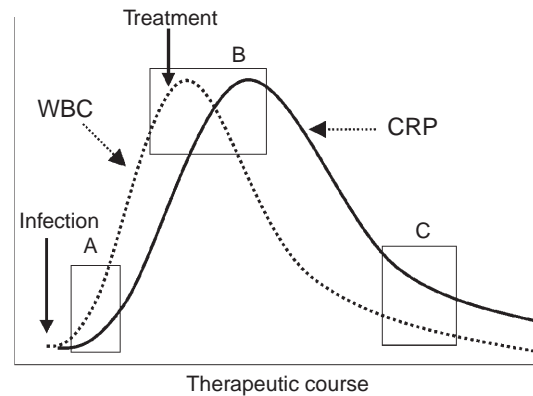


Fig.4. Change in WBC and CRP by manifestation and treatment of bacterial infection.

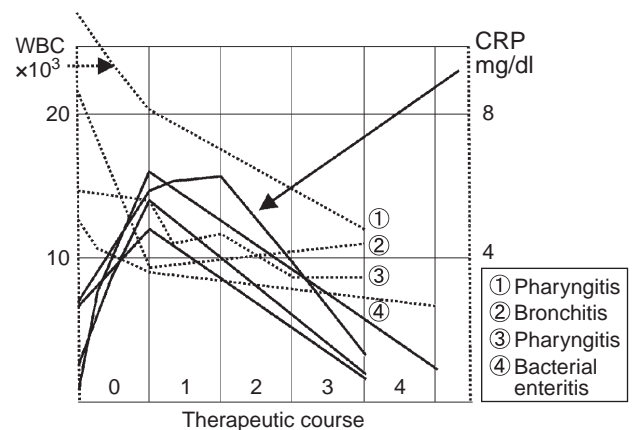


Fig.5. Change in WBC and CRP by manifestation and treatment of bacterial infection.

The figure presents changes in WBC and CRP from four patients who could be repeatedly examined, beginning at the initial state of infection.

Based on these results, the repeated simultaneous measurement of WBC and CRP was considered effective for identifying the time of infection, making an early determination of therapeutic effect, and understanding the severity of disease.

6) Data from the instrument were found effective in assisting the clinician in understanding the state of disease and controlling therapy for outpatients. The data was also effective in the diagnosis of bacterial enteritis, determining the complication of bacterial infection in patients with febrile convulsion, and controlling lower respiratory tract infection and influenza-like disease.

7) The effects of the quantitative and qualitative examinations of CRP were compared in 201 patients.

The results, presented in Table 6, showed that quantitative analysis was better in terms of (1) the evaluation of the severity and course of inflammation and (2) providing convincing evidence when explaining the state of disease to a patient's family.

	CRP quantitative	>	CRP qualitative
Determination of severity	⊙	>	△
Determination of course	⊙	>	×
Combination with CBC	○	>	×
Persuasion	⊙	>	○
Convenience of blood collection	⊙	=	⊙
Speed	○	<	⊙
Cost	○	<	⊙

Table 6. Comparison of the effects of CRP quantitative and qualitative methods.

8) The economic benefit of the instrument was confirmed in about 45% of the patients. The effects include avoidance of X-p (54%), avoidance of DIV (23%), and better drug selection (17%). The economic effects we measured are shown in Fig.6.

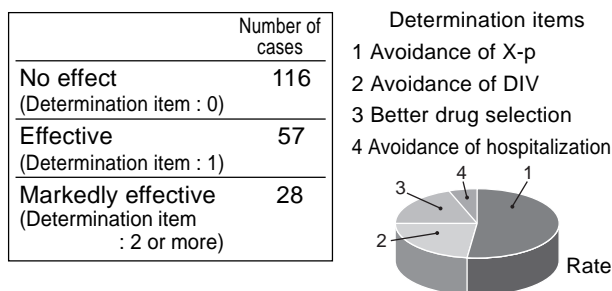


Fig.6. Economical effect of installation of simultaneous repeated measurement of WBC and CRP.

4

Discussion

4.1 Effects of painless blood collection method and quick measurement.

Using the Microlet™ to collect blood from a fingertip has the following advantages over the conventional method of blood collection from the earlobe.

1. The infant is comforted by being able to sit on the mother's lap while blood is collected.
2. Infants better tolerate having a finger tip restrained than having the head restrained or the ear touched.
3. A fingertip provides a more stable blood collection site than the earlobe.

Blood collection from a fingertip has disadvantages as well : a fingertip of babies of less than 2 to 3 months of age is too small and cannot be restrained due to the grasping reflex. Such patients have blood collected from their hypothenar eminence or heel using the same technique. When a patient is about 6 years old or older, the sensation of the fingertips has developed and pain experienced during blood collection increases, although it seems tolerable. In such a case, blood may be collected from the earlobe, although other blood collecting devices should be used since the Microlet™ does not prick the earlobe deeply enough.

Use of the LC-270 CRP and the painless blood collection technique from a fingertip dramatically changed the ways examinations were performed in our hospital. Previously, minimal examinations based on clinical experiences were performed to avoid the pain associated with collecting blood samples. However, since the introduction of the instrument and blood collecting technique, CRP measurement and CBC have come to be actively performed, which has led to an improvement of the understanding of the course and state of disease. This allows pediatricians to make more accurate decisions.

4.2 Effects on outpatient management

The effects of the instrument on outpatient management can be divided into (1) screening effect, (2) effect on diagnostic and therapeutic decisions, and (3) effect on understanding the state of disease.

(1) Screening effect

This effect was especially evident in the screening of asymptomatic and rapidly progressing serious bacterial infection in infants. When early diagnosis of urinary tract infection is required, it is effective to examine CRP and CBC with this instrument first and then confirm the result with urinalysis because urinalysis and urinary culturing

cannot be performed quickly. Many of the present cases with bacterial meningitis and urinary tract infection arrived at our hospital within 24 hours from the onset of fever. A considerable number of cases could not be handled by the conventional system that entrusts blood testing to outside laboratories, because they arrived immediately before the consultation time was over, on Saturdays, or immediately before holidays. This effect of screening for serious bacterial infection in infants is one of the most significant benefits of the instrument.

(2) Effects on diagnostic and therapeutic decisions

Data from the instrument was useful for differentiating viral from bacterial diseases, etc. This reduced unnecessary use of X-ray examinations and antibiotics for mild diseases, such as bronchitis with mild inflammation. The data was also effective in diagnosing early Kawasaki disease when symptoms did not yet meet the conventional diagnostic criteria.

(3) Effect on understanding the state of disease

Data provided by the instrument was especially effective for estimating the duration of infection and determining the effects of therapy for bacterial infection (Fig.7).

Thus it allowed appropriate medical treatments (X-ray examination, DIV, and hospitalization, etc.) at an appropriate time. These effects cannot be obtained by conventional qualitative and quantitative examinations of CRP or general blood testing alone. It is fair to say that they can be obtained for the first time by the immediate simultaneous measurement of CRP and other blood parameters by the combined use of the LC-270 CRP and the technique for collecting extremely small-volume blood samples.

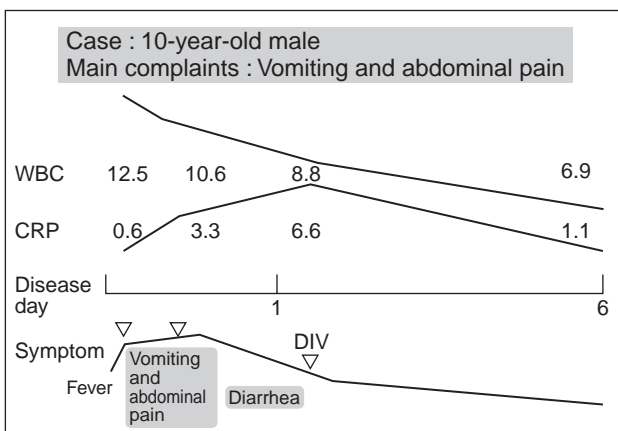


Fig.7. Clinical progress and final value for bacterial enteritis.

4.3 Comparison between qualitative and quantitative examinations of CRP

The most convenient and widely-used examination for determining the severity of inflammation is the qualitative examination of CRP. Table 3 compares the effects of qualitative and quantitative examinations of CRP. Although this is a single-facility, uncontrolled study, the table seems to outline the differences between the two examinations.

For the effects on outpatient management, the qualitative examination of CRP provides a screening effect, but was not as effective in determining diagnosis and treatment or understanding the state of disease. The advantage of the quantitative examination of CRP seemed quite evident.

4.4 Economic benefits of the instrument

Table 4 shows the number of patients who met each of the four economic effect-determination criteria, although this was a single-facility study. The reduction of medical costs by reducing the use of X-ray examinations and antibiotics is one of the demands of the times. This issue seems important and should be examined in a multi-center study. Data from our pediatric outpatients and data on the clinical effects of the instrument will be valuable in such a study.

5

Conclusion

The effects of the immediate simultaneous measurement of CRP and WBC using the LC-270 CRP can be summarized as follows:

- 1) Clinical practice: Quicker and more accurate medical decision-making and treatment.
- 2) Patient benefits: Deeper understanding of medical treatment by obtaining important medical information.
- 3) Economic advantages for both medical institutions and patients.

Since these effects improve medical technology and convenience for both medical institutions and patients, the LC-270 CRP is expected to contribute to the improvement of medical quality.

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